GENDER DIFFERENCES IN CHEMOSENSORY FUNCTION

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Abstract

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This thesis consists of two studies, in which gender differences in nasal chemosensory function are investigated. The first study assesses odor identification ability in a population-based sample, varying from 45 to 90 yrs, screened for cognitive impairment and severe olfactory dysfunction. Results show that women are generally better than men at identifying odors, but there is no significant interaction of gender by age. Although odor identification is influenced by semantic memory and cognitive speed, these cognitive factors are unlikely to cause the observed gender difference in odor identification. The second study investigates chemosensory perception in men and women by assessing event-related brain potentials, and perceptual ratings for an odorant, which varies in concentration and olfactory/irritating properties. The results display a generally larger cortical response in women than in men, beginning from about 350 ms after stimulus onset. Women report higher perceived intensity and unpleasantness at the highest stimulus concentration, and a steeper psychophysical function, than do men. The results indicate that stronger cortical responses of nasal chemosensory stimuli provide a neural basis for stronger supra-threshold perception in women than in men, which might enhance odor identification performance. The nature and causes of these gender-differences in nasal chemosensory function are discussed.

This thesis for the licenciate degree is based on the following studies:

Larsson, M., Nilsson, L-G., Olofsson, J.K., & Nordin, S. (2004). Demographic and cognitive predictors of odor identification: Evidence from a population-based study. *Chemical Senses, 29,* 547-554.

Olofsson, J.K., & Nordin, S. (2004). Gender differences in chemosensory perception and event-related potentials. *Chemical Senses, 29,* 629-637.

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Jonas Olofsson

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INTRODUCTION

"…a complete, comprehensive, understanding of odor… may not seem a profound enough problem to dominate all the life sciences, but it contains, piece by piece, all the mysteries."

-Lewis Thomas

Although not often recognized, the ability to perceive smelling, tasting, and irritating chemicals is very important in our everyday lives. In order to detect health-hazardous chemicals in food and air, we use mainly our nasal chemoreceptors, which mediate information about the chemical environment through the olfactory and trigeminal nerves. By powerful food aversion learning, the chemical senses keep us from ingesting food items that has previously been associated with illness (Jacobsen, Bovbjerg, Schwartz, Andrykowski, Futterman, Gilewski, et al., 1993). In a modern society, the abilities to detect, recognize, and discriminate odors are fundamental and important tasks in food behaviour and nutrition, and the chemical senses influence our perceived life quality and psychological well-being (Hummel & Nordin, 2005). Some researchers emphasize the social and sexual roles of the chemical senses (Gower & Rupareila, 1993). Individual differences in olfactory abilities are pronounced, and depend on various biological, cognitive and social factors. Differences between men and women have been studied in a variety of settings. However, there seems to be no definite conclusion on the influence of gender on olfactory abilities (Brand & Millot, 2001).

The present work concerns nasal chemosensory perception and cognition in men and women. In two studies, possible gender differences in various aspects of chemosensory function are investigated. The first study (Larsson, Nilsson, Olofsson & Nordin, 2004) concerns the ability to identify household odors in a four-alternative forced-choice task. Gender differences in this task are assessed by results from a population-based investigation of 1906 healthy individuals, divided in five age cohorts of the adult life-span (45-90 yrs). A possible interaction between gender and age, as well as cognitive factors influencing odor identification ability are also assessed. In the second study (Olofsson & Nordin, 2004) gender differences in odor perception are addressed by a combined neurophysiological and perceptual assessment of healthy young adults. A background and a review of relevant literature is provided in the first section of this work: This includes an introduction to nasal chemosensory physiology and common testing procedures to assess nasal chemosensory function. A brief review over gender differences in perception and cognition, as well as a description of the event-related potential (ERP) technique used in Study 2 is provided. The present studies are presented, and the results are discussed in the context of previous research. The prospects and the pitfalls of studying gender differences in chemosensory function are discussed from a methodological and a clinical perspective. The reader is referred to the two original articles for a more detailed description of the present studies.

BACKGROUND

Biological Basis of Nasal Chemoreception

The ability of an organism to respond to changes in the environment is fundamental to the organism's survival. We rely preferentially on our senses of vision and audition in our interaction with the environment: physical movement and shifting of attention is normally guided by visual and auditory cues. However, the chemical senses are for many animals the primary windows to the external world (Ache, 1991). The ability to perceive chemical substances in the environment is regarded as perhaps the phylogenetically oldest perceptual ability of living organisms. Even bacteria have specialized mechanisms for detecting environmental chemicals. Animals can perceive chemicals in the environment if there are receptor cells that translate the chemical environment into electrical impulses of afferent nerves. The nervous systems accomplish this in a variety of ways that differs between the chemical senses, and between species (Doty, 2001). Communication of biologically relevant information through the chemical senses is present in many species, regulating e.g. mating behaviour. It has been argued that this "pheromonal" communication is also relevant for humans: Although we probably lack a functional vomeronasal organ, which in other species serves for pheromonal perception, it is likely that human behaviour and psychological state can be influenced by odorous steroids. Two structurally related odorous steroids, androstenone and androstadienone, do potentially function as pheromones in humans (Jacob & McClintock, 2000; Lundström, Hummel, & Olsson, 2003; Hummel, Krone, Lundström, & Bartsch, 2005; see also Doty, 2003b). The present studies, however, concern non-pheromonal odorants.

The olfactory sense is activated when chemical molecules reach the olfactory neuroepithelium at the top of the nasal cavities. The olfactory neuroepithelium contains approximately 6 million bipolar receptor cells. The receptor cells have cilia branching out to the outer layer of the epithelium. The cilia contain the receptors that interact with the odorant. Different receptor cells are tuned to be responsive to different classes of odors, depending on their molecular structure. Cilia of the receptor neuron are depolarized by an olfactory stimulus, and summarize on the receptor cell body to evoke an action potential. The axons of the receptor cells project through the cribiform palate, a bone that separates the nasal cavity from the brain cavity, to the glomerular layer of the olfactory bulbs. For a single odorant, many activated receptor cells converge on a smaller number of glomerular cells in the olfactory bulb, giving rise to patterns that has been assumed to reflect qualitatively distinct odor sensations (Doty, 1991). Through both inhibitory and excitatory processing in the olfactory bulb, activation is transduced by the olfactory nerve (CN 1) to the olfactory cortex located in the medial temporal lobe. Perceptual and cognitive processing of chemosensory information involves several subcortical and cortical areas, which vary according to the perceptual properties of the odorant, and the task performed by the participant (Royet & Plailly, 2004; Savic, Gulyas, Larsson, & Roland, 2000).

The trigeminal nerve (CN 5) has chemosensory receptors that innervate the nasal cavity, as well as the oral cavity and the eye (Silver & Finger, 1991; Tucker, 1971). Trigeminal activity causes stinging, cooling, warm, and pungent sensations, sensations which are categorized as irritation. It is often activated together with olfactory or gustatory stimuli (Doty, 1978) adding a pungent sensation to many food products, such as chilli (containing the irritant capsaicin) or sparkling beverages (containing CO2). Chemosensory irritation can be evoked by most environmentally occurring odorants, given that it is present above a certain concentration (Doty, Brugger, Jurs, Orndorff, Snyder, & Lowry, 1978). For example, the odorants of paint, tar, and nail polish are apart from their olfactory features likely to evoke an irritating sensation in the nasal cavity. The nasal innervations of the trigeminal nerve enable chemical stimulation of free nerve endings in the nasal mucosa. Chemosensory irritation is mediated by C fibers and A-delta fibers (Hummel, 2000). It projects to e.g., the insula and amygdale via rostral spinal nuclei and the thalamus (Hummel & Livermore, 2002).

The present empirical studies concern orthonasal (through the nostrils) chemosensory stimulation of the olfactory nerve (Study 1) and by varying concentrations of a "mixed" olfactory/trigeminal stimulus (Study 2). The term "odorant" will here refer to all chemosensory nasal stimulants. The "olfactory/trigeminal" distinction denotes the two different kinds of sensations.

Human olfactory function

"…the organic sublimation of the sense of smell is a factor of civilization."

- Sigmund Freud

The olfactory sense has been neglected by many philosophers and experimental researchers for a long time. Plato and Aristotle considered olfaction as a less noble sense than vision and audition. The conception of olfaction as a primitive and crude sense is since that time evident along western intellectual history (Le Guérer, 2002). The quote from Sigmund Freud (cited by Le Guérer, 2002) demonstrates Freud's view of olfaction as a primitive sense: As olfaction is associated to sexuality and emotions, Freud argued that in a modern society, olfaction needs to be suppressed (by Freuds terminology, sublimated). Some modern psychological researchers have also de-emphasized the importance of olfaction in humans: MIT professor Steven Pinker has stated "…the sense of smell is of relatively minor importance in the normal life of the civilized man" (cited by Lorig, 1999). Le Guérer (2002) argues that the relative lack of psychological research on olfaction when compared to the other senses in part depend on a cultural hierarchy, where olfaction is considered emotional and subjective, and hence inferior to the more "intellectual" visual and auditory senses. According to a survey, university students regard the sense of olfaction as the least important sense (Van Toller, 1999).

However, given their fundamental evolutionary significance, a subtle but never the less important role of the chemical senses might be expected also in human behaviour. Indeed, the use of perfumes and pleasant-smelling smokes (during religious ceremonies) served very important societal functions already in ancient societies (Doty, 2003a). The importance of spices in western civilization can be illustrated by the fact that during the siege of Rome in A.D. 408, a ransom of 3000 pounds of pepper was demanded for the city (Doty, 2003a). The importance of olfaction has been recognized in contemporary studies on consequences of olfactory dysfunction for food appreciation and nutrition, perceived life quality and subjective well-being (Van Toller, 1999; Hummel & Nordin, 2005). It has been argued that the sense of smell plays an important role in human reproduction – e.g., the percieved pleasantness of an other person's body odor potentially serve as a cue about this persons' genetic setup (Jacob, McClintock, Zelano, & Ober, 2002). Recent studies show evidence that, in some cases, primates' olfactory sensitivity are comparable to the olfactory sensitivity of rats and dogs, species recognized for their advanced olfactory abilities (Laska, 2000). The olfactory sensitivity in humans has been found to be superior to the most advanced technical instruments (Tagaki, 1989). An increasing body of research on human olfaction indicates a tendency to overcome the relative lack of knowledge about the olfactory sense (for reviews, see Doty, 2001; Royet & Plailly, 2004; Hummel & Nordin, 2005).

Behavioural assessment of human olfaction

Olfactory function can - as the functioning of other sensory systems - be assessed in various ways, ranging from basal sensory processes to more cognitive tasks. Olfactory sensitivity is often assessed by psychophysical evaluation of detection or discrimination ability for weak odor concentrations. These methods are in general based upon Fechner's "method of limits" or "method of constant stimuli" (described in Gescheider, 1997). For a review of psychophysical olfactory testing, see e.g. Doty and Laing (2003).

Odor identification refers to the participant's ability to retrieve the correct name for odors presented, often by means of a forced-choice procedure with several response alternatives. Several different odor identification tests have been developed for use in different populations and age groups (e.g., the UPSIT, Doty, Shaman, & Dann, 1984; the SOIT, Nordin, Brämerson, Lidén, & Bende, 1998; the SDOIT, Anderson, Maxwell, & Murphy, 1992). Adjusting the odorants to fit cultural experiences is necessary. For example, the UPSIT uses root beer (a soft drink), an odorant that are less recognized by the Scandinavian population. Odor Identification tests have been shown to have significant clinical utility as a test of olfactory function. It is also a sensitive test for detecting neurodegenerative diseases, such as Alzheimer's disease (Morgan, Nordin, & Murphy, 1995). Despite of the practical utility of the test, little is known about what cognitive factors are demanded for high odor identification performance. A certain degree of olfactory sensitivity is obviously needed, as well as ability to discriminate odor intensity and quality (Doty, Smith, McKeown, & Raj, 1994). Identifying an odor relies also on semantic memory, since the task involves retrieving a verbal label that is associated with the sensation (Öberg, Larsson, & Bäckman., 2002).

Episodic memory tests typically employ visual stimuli. Less is known about our ability to memorize odors. Since odorants can evoke vivid autobiographical memories, one might assume that olfactory memory is more proficient than memory for other senses. Indeed, an encoded odor memory trace is more stable over time than visual memories (Engen & Ross, 1973). However, the ability to successfully encode an odor is influenced by semantic and emotional associations to the odor stimuli (Larsson & Bäckman, 1993). Basic detection and discrimination sensitivity does also influence the odor memory performance (Doty et al., 1994).

Assessment with ERPs

Neural substrates of odor perception and cognition have mainly involved hemodynamical (fMRI/PET) and electrophysiological (ERP) measurements during olfactory perception and cognition. In the second study of this thesis, ERP responses to odors are recorded. The ERP is the change in the brain's electrical activity that follows a perceptual or cognitive event. The ERP is usually too small to be identified in all other activity recorded from the brain, but the patterns associated with the stimulus can be measured if it is repeated several times. Each time the stimulus occurs the evoked potential will be the same, but the other brain activity will vary. By averaging several recordings, the cyclic EEG activity and the random noise tend to cancel itself out. Thus, averaging many identical stimulus presentations improves the signal-to-noise ratio in the ERP. After averaging, what remains of the measurements is the response to the stimulus, which is the ERP: A wave consisting of positive and negative deflections of the brains' electrical activity that is time-locked to the onset of a certain stimulus. The scalp electrodes register mainly electrical activity generated when there is synchronous summation of parallel electrical dipoles in large populations of neurons. This occurs mainly in the post-synaptic potentials in the dendrites of the neocortex (Westbrook, 2000). These are often perpendicular and close to the scalp electrode, which makes it possible to measure this electrophysiological activity. The positive or negative orientation of the ERP deflection depends on the orientation of the electrical current dipole. Dendrites receive input in several layers of the cortex. If the synapses occur in a layer close to the electrode (such as layer 2), there will be a negative deflection of the ERP, and if it occurs in a more remote layer (such as layer 4) there will be a positive deflection of the ERP. Therefore, the size of these deflections is measured by comparing the largest point of a certain deflection with a pre-stimulus interval (usually 200<500 ms before stimulus onset) as a baseline. This measure (referred to as the amplitude) reflects the amount of neural activity at a particular point in time. The time from stimulus onset to the peak of the deflections (referred to as the latency) is used as an index of timing of neural processes.

The shape of the ERP depends on stimulus characteristics and task structure, and it is also influenced by individual differences in psychological and physiological parameters (see Rugg & Coles, 1995, for ERP methods applied in cognitive psychology; Polich & Kok, 1995, for a review of influences of cognitive and biological variables on ERPs). The components of the human ERP can be used to study what happens in the brain during complex psychological processes such as attending to some stimuli and ignoring others. Chemosensory ERPs (CSERPs) was first recorded in humans by Kobal (1981), who developed a device for presenting odorants with a rapid on- and offset in a constant stream of clean air, which is necessary to obtain a CSERP response. Due to problems of adaptation in the chemical senses, stimulus presentation is more limited in CSERPs than in other sensory systems. During CSERP recording sessions, single chemosensory stimuli are presented using a long (30-60s) inter-stimulus interval. In contrast to brain imaging techniques such as fMRI and PET, the ERP does not assess brain function indirectly by blood flow measurements in different brain regions, but it provides a temporally precise index (ms range) of activity in large populations of neurons.

Morphology and neural substrates of the CSERPs

The CSERPs, in a similar vein as the ERPs from other sensory systems, have a wave-like shape, consisting of a series of positive and negative voltage deflections from a pre-stimulus baseline. The CSERPs are typically smaller than the ERPs of other senses, which make it somewhat more difficult to distinguish the CSERPs from noise. A common nomenclature for CSERP components is to use the denotations P1 (first positive), N1 (first negative), P2 (second positive) N2 (second negative) and P3 (third positive) for the deflections typically seen. The chemosensory P1 is often as small as the level of noise, and it is therefore seldom subject to investigation. A functional significance of the N2 has not been successfully established. In most experimental settings, the N2 can simply be described as a deflection towards baseline between the components P2 and P3 (although see Krauel, Sojka, Pause, & Ferstl, 1999, for a psychological interpretation of N2 during a "mismatch" paradigm). Therefore, the P1 and N2 are not discussed further.

The CSERP wave is dominated by the N1 and a late positive complex, consisting of the P2 and the P3. The morphology of the CSERP is quite similar across studied odorant qualities, concentrations, and stimulus protocols (Hummel & Kobal, 2001). This makes it problematic to claim that the components reflect distinct psychological processes. Although such claims has been made (e.g., Pause, 2003), these arguments are often based on analogies with ERP findings in other sensory modalities, and should be regarded as hypotheses. However, Hummel and Kobal (1992) showed that different odorants produced somewhat different topographical distributions of the CSERP amplitudes across the scalp, even when adjusting for general differences in ERP amplitudes. This indicates that the CSERPs reflect partly different neural generators in the processing of different odorants.

The N1 and P2 have been shown to increase in amplitude, and to decrease in latency when stronger chemosensory stimulus concentrations are presented (Tateyama, Hummel, Roscher, Post, & Kobal, 1998; Covington, Geisler, Polich, & Murphy, 1999). The olfactory N1 and P2 are generally larger in people that have high olfactory detection sensitivity (Murphy, Nordin, de Wijk, Cain, & Polich, 1994). The N1 latency seems to be the parameter that is most sensitive to changes in stimulus magnitude, and correlates most strongly with odor detection sensitivity (Pause, Sojka, & Ferstl, 1997; Covington et al., 1999; Tateyama et al., 1998).

It is generally assumed that the P3 is unspecific with regard to sensory modalities (Geisler, Morgan, Covington, & Murphy, 1999). The dominating psychological framework for explaining the P3 is the "context-updating" model (Donchin & Coles, 1988). According to this model, the P3 reflects an updating of the internal model of the external environment, elicited by a relevant change in this environment. The P3 can be evoked by a rare target stimuli in a train of common non-targets (the oddball paradigm) but also through the use of one standard stimulus if the inter-stimulus interval is long and the participant is attending to the stimulus, ensured by having the participant evaluate the stimulus (e.g., by button-pressing, counting; Mertens & Polich, 1997). Although the N1 and P2 are sometimes called "sensory components" while the P3 is regarded a "cognitive component" (Murphy, Morgan, Geisler, Wetter, Covington, Madowitz, Nordin & Polich, 2000; Hummel & Kobal, 2001), the shift from predominantly exogenous to endogenous processing across the ERP components is likely to be continuous. Although not extensively studied, olfactory ERP components have been demonstrated to be influenced by attention: Amplitudes are larger when the participant is attending to the stimulus (Geisler & Murphy, 2000).

For trigeminal stimulation in CSERP studies, CO_2 is commonly used, since it is a pure irritating stimulus with no olfactory quality. The trigeminal ERP is similar in shape to the olfactory ERP, and is influenced by the same factors as the olfactory ERP. However, the trigeminal ERP responses are less diminished than the olfactory ERPs when participants are told to ignore the stimuli (Geisler & Murphy, 2000).

The nature of the late positive complex (LPC) of the CSERP (P2/P3) is a matter of debate, due to the difficulty of separating the P2 from the P3. Often, the LPC has only one visible peak. In those cases, it is sometimes called a P2, and sometimes it is called a P3. Some authors have argued that the olfactory P2 is overshadowed by a P3 (Pause, Sojka, Krauel, Fehm-Wolfsdorf, & Ferstl, 1996). Using trigeminal stimuli, the LPC is presumably dominated by a large P2, which overshadows a smaller P3. In mixed olfactory/trigeminal stimuli, the LPC consists of multiple generators in the olfactory and trigeminal system. Therefore, in Study 2, we denote the LPC as one "P2/P3" component. Recent data from our laboratory suggests that the LPC evoked by pyridine consists of a P2, which is followed by a smaller P3 (Olofsson, Ericsson, Murphy, & Nordin, 2005).

The neural generators of the CSERP components are scarcely investigated with magnetic source imaging techniques (Kettenman, Jousmaki, Portin, Salmelin, Kobal, & Hari, 1996; Kettenman, Hummel, Stefan, & Kobal, 1997). Although the small number of studies, and the methodological problems of localizing electrical dipoles from the scalp should be emphasized (Hummel & Kobal, 2001), tentative conclusions on the neural generators of ERPs can be made: The olfactory N1 component of the ERP is likely to be generated in the anterior-central parts of the insula (Kettenman et al., 1997), a neocortical area which receives input from primary olfactory cortices. In fMRI experiments, this area has been shown to be strongly activated by olfactory, and by mixed olfactory/trigeminal stimuli. The following positive component (P2) is likely to be generated in the superior temporal sulcus (Kettenman et al., 1997). For trigeminal stimuli, the neural generators of ERP components are less investigated than the olfactory ERP generators. In an early study, the P2 evoked by CO_2 was located in the secondary somatosensory area (Huttunen, Kobal, Kaukoronta, & Hari, 1986). However, using fMRI technique, Hummel and colleagues (Hummel, Doty, & Yousem, 2005) did not show activation in this area when presenting CO2. Instead, they found evoked activity in several cortical areas that either overlap with areas activated by odors or are adjacent to those areas, including the superior temporal gyrus and ventral insula.

Gender differences: an overview

In the history of western science, the view of women, when compared to men, displays some similarities with the view of olfaction in comparison to the other senses. Differences between men and women in psychological abilities were proposed already in the writings of the ancient Greeks: In Plato's (427-347 BCE) story of creation, Timaeus, the first generation of mankind consisted only of men. Those who in their lives were guided by reason, were re-borne as men, and those who let emotions and sensations rule were re-borne as women (Tuana, 1993). Aristotle (384-322 BCE) agreed on this association of men with reason and women with sensation/emotion, and provided the first biological explanation for presumed differences between the sexes: He believed that women are physically colder than men. Aristotle associated heat and energy with perfection, as heat was necessary in order to bring form to raw matter. Aristotle used the presumed relative cool of women as evidence of women's presumed inferiority in character, and speculated that women were conceived of either too old or too young mothers (Tuana, 1993). Although this position might seem extreme and obsolete, similar conceptions of biology-based gender differences are present through the history of science. For example, Charles Darwin (1809-1882) argued that women have superior abilities in perception and "intuition", which was conceived of as phylogenetically old abilities. However, according to Darwin, women were not as proficient as men in their ability to reason, which he considered to be a phylogenetically more recent, and thus nobler, trait (Tuana, 1993). This brief review suggests that gender differences in western intellectual history have been conceived of through a cultural hierarchy, where women have been associated with sensory/emotional abilities, and men with intellectual, cognitive abilities. Since gender differences by tradition belongs to the arena of social policy, as well as to the arena of scientific enquiry (Halpern, 1997), it is thus not surprising that modern investigations of psychological or biological differences between the sexes receive large attention and controversy wherever noted.

Contemporary research on gender differences

Since the 1960's, gender differences in cognitive and sensory functions have received increasing interest (see e.g., review by Velle, 1987). Gender differences in cognition have been shown in many empirical studies, although the differences are often small. Among the most consistent findings is that women perform better than men on verbal tasks, whereas men perform better than women in visual-spatial tasks. Indeed, many studies show large differences between the sexes. Men are better on mental rotation tasks, and women are better on verbal and perceptual speed tasks (Masters & Sanders, 1993; Maitland, Interieri, Schaie, Whillis, 2000). Halpern (1997) noted exceptions from this generalized notion; men perform somewhat better than women on analogies and women perform somewhat better on memory for location and mirror tracing tasks. Men's advantage is largest in tasks requiring manipulation of visual-spatial information, whereas women's advantage is largest in tasks requiring access to, and production of verbal information (Hyde & Linn, 1988).

Gender differences have been reported for every major sensory system (Velle, 1987). Where a gender difference is noted, women most often display higher acuity. In studies of the auditory sense, women display lower threshold (i.e., higher acuity) than men during different ages, and with larger gender differences in high frequencies (Corso, 1959; McGuinness, 1972; Cassidy & Ditty, 2001). The findings have to some extent been corroborated by findings in brain-stem ERPs: Women show larger amplitudes than men (Michalewski, Thompson, & Patterson, Bowman, & Litzelman, 1980). However, it is not known to what extent these findings are influenced by gender differences in anatomical parameters (Don, Ponton, Eggermont, & Masuda, 1993). Sensory ERPs do not typically show gender differences (J. Polich, personal communication), although Polich and Conroy (2003) found higher amplitudes in women than in men for the cognitive P3 ERP component. The findings of women's advantage in auditory sensitivity are mainly related to detection threshold: Ability to discriminate pitch has been reported not to display this women's advantage (McGuinness, 1972). Gender differences in behaviour related to auditory stimulation has been reported: Girls and young women have displayed less tolerance to noise than boys and men in comparable age groups (McGuinness, 1972). However, it can be argued that tolerance to noise reflect not only sensory acuity, but also various psychosocial factors. In vision, gender differences have been reported in adult participants (Burg & Hulbert, 1961; Burg, 1966; McGuinness, 1976), displaying somewhat better sensory discrimination performance in men. Thus, gender differences in visual and auditory perception are common findings, but the results are not conclusive.

Gender differences in the nasal chemical senses

The status of gender differences in chemosensory function has recently been described as somewhere "between evidence and enigma" (Brand & Millot, 2001), despite many reports of a female advantage. Gender-related differences in odor perception were reported by Toulouse and Vaschide in 1899, who found lower detection thresholds (i.e., higher sensitivity) in women than in men. This finding has been corroborated by several more recent investigations using different odor substances for establishing detection thresholds and discrimination which is considered to reflect olfactory sensitivity at a peripheral level. (Schneider & Wolf, 1955; Koelega & Köster 1974; Wallace, 1977). These differences are not always obtained (e.g., Öberg et al., 2002), but women are always superior when a gender difference in olfaction is noted (Brand & Millot, 2001). It was suggested by Le Magnen (cited by Koelega & Köster, 1974) that the gender difference is largest for odors with "biological relevance" (e.g. having pheromonal properties). While this notion has not been fully established (Koelega & Köster, 1974), there have been several reports of gender differences in perception of odorous steroids: Steroids alter the physiological states of men and women differently, in a way that is related to states of mood and alertness (Jacob & McClintock, 2000; Jacob, Hayreth, & McClintock, 2001). Gender differences have been reported also in olfactory tasks that involve more cognitive elaboration of the olfactory information. Studies on gender differences in the ability to correctly identify odors, have shown higher performance in women than in men (Cain, Gent, Goodspeed, & Leonard, 1988; Doty, Shaman, Applebaum, Gibertson, Sikorski, & Rosenberg, 1984b), which has been related to semantic factors (Öberg et al., 2002).

Murphy et al., (Murphy, Schubert, Cruishanks, Klein, & Nondahl, 2002) found higher prevalence of olfactory loss in older men in a population-based study of adults aged 50 years and older, which might indicate an interaction between gender and age. This was also reported by Ship and colleagues (Ship, Pearson, Cruise, Brant, & Metter, 1996), who found that the ability to identify odors was compromised earlier in life for men than for women. Further support for this has also been presented by means of olfactory ERPs (Morgan, Covington, Geisler, Polich, & Murphy, 1997). However, a Swedish population-based study on odor identification ability revealed lower general performance in men than women, and lower performance in older participants compared to younger participants, but no interactions between gender and age (Brämerson, Johansson, Ek, Nordin, & Bende, 2004).

Several studies have shown that women tend to perform better than men on episodic odor memory tasks, which might be due to influences of verbal/semantic factors (Choudhury, Moberg, & Doty, 2003; Larsson, Lövden, & Nilsson, 2003; Öberg, et al., 2002). However, knowledge is sparse regarding relationships between demographic factors, cognitive abilities, and odor identification performance.

In comparison to detection and identification of odors, perceived intensity and valence have received relatively little attention. One ambitious study on this topic used data from the National Geographic Smell Survey, which was inserted in copies of the National Geographic magazine, using "scratch-and-sniff" items (Wysocki & Gilbert, 1989). The results revealed higher intensity ratings by women than by men for mercaptan, rose, isoamylaceate and eugenol. However, despite an impressive number of respondents (1.42 million) to the survey, this represented a modest response rate of 13%. Furthermore, women were more likely to return the survey, indicating a possible selection bias (56% of the respondents, but only 41% of the readers were female). In a laboratory study, in which 10 concentrations of the odor pyridine were presented, women were found to report unpleasantness at lower concentrations (lower unpleasantness thresholds) than men and gave higher unpleasantness ratings for suprathreshold concentrations (Broman & Nordin, 2000). Pyridine is regarded as an unpleasant odor, and it evokes a trigeminal sensation at concentrations significantly higher than the olfactory detection threshold (Berglund & Shams Esfandabad, 1993). Trigeminal activation by nasal stimulation has been less investigated than pure olfactory sensations. However, the trigeminal sense does also seem to be more sensitive in women than in men: Commetto-Muniz and Noriega (1985) demonstrated more intense perception of $CO2$ pungency in women when employing both magnitude estimation and magnitude matching. Two studies have shown higher sensitivity in women for detection of the trigeminal stimulus $CO2$ (Schusterman, Murphy, & Balmes, 2003; Schusterman & Balmes, 1997), however other studies have reported no gender difference (e.g., Cain & Murphy, 1980; Hummel, Futschik, Frasnelli, & Huttenbrink, 2003). Recordings of chemosensory CSERPs have yielded higher amplitudes in women than in men in response to non-irritating odor stimulation (Becker, Hummel, Piel, Pauli, Kobal, & Hautzinger, 1993; Evans, Cui, & Starr, 1995; Morgan et al., 1997). This has also been reported for CSERPs to trigeminal stimuli (Hummel, Bartz, Pauli, & Kobal, 1998). Mixed olfactory/trigeminal stimuli had not been investigated in the context of gender differences at the time of the present studies.

RESEARCH OBJECTIVES

The present two studies approached the question of gender differences in chemosensory function in a broad respect, using both neurophysiological and behavioural measures. The first study concerned an olfactory identification task that depended both on olfactory perception and cognitive function. Differences related to gender and age were assessed. Attempts were also made to interpret performance on the odor identification task from cognitive measures.

The second study investigated evoked brain activity and perception in response to three concentrations of the odorant pyridine, which activates both the olfactory and the trigeminal nerve. Given that pyridine activates the trigeminal nerve over a certain threshold, and that the irritation dominates and typically even suppresses the olfactory intensity (Cain & Murphy, 1980; Cometto-Muniz & Hernadez, 1990), one aim was to investigate possible gender differences in the transition from olfactory perception to trigeminal perception as the concentration of pyridine varied. The inclusion of perceptual ratings was motivated by a relative lack of knowledge about how men and women might differ in terms of their supra-threshold perception of odors (Brand & Millot, 2001).

EMPIRICAL STUDIES

Study 1: Demographic and cognitive predictors of odor identification: Evidence from a population-based study

The major aims of this study were to address gender- and age-related differences in odor identification, and to assess cognitive influences that may contribute to successful identification. Gender differences in performance in odor identification were assessed across the adult lifespan (45-90 yrs.) by means of the Betula prospective cohort study: A population-based study focusing on memory, health and aging (Nilsson et al., 1997). The data was derived from the third wave of the Betula study (collected 1998-2000), carried out in the city of Umeå, containing various assessments in cognitive tasks. The odor identification test used in the Betula procedure is the Scandinavian Odor Identification Test. This test was developed by Nordin and colleagues (Nordin et al., 1998) for a Scandinavian population. The stimulus material contained 13 household odors: anise, apple, cinnamon, clove, juniper berry, lilac, lemon, orange, pine-needle, tar, violet, and vanilla. This differs from the original test material, which contained sixteen odors. In the version used in the present study, three odors that have been shown to be significantly detected by anosmics – thus having a significant trigeminal impact (Nordin et al., 1998) – were excluded for testing. The response alternatives were also changed from the original test: In order to make the test more difficult and thus avoiding ceiling effects, the three incorrect response alternatives of the original test were replaced by alternatives that were perceptually more similar to the correct alternative (e.g., "lemon" was one of the incorrect alternatives for orange). Additional tests were selected to assess cognitive function in different domains, including semantic memory, cognitive speed, and executive functioning (see Larsson et al., 2004, for a detailed description).

Since the study's aim was to investigate demographic and cognitive factors determining successful odor identification in healthy adults and elderly, anosmic and cognitively impaired participants were not of interest. Excluded from the data set were thus participants who scored at chance level in the odor identification test (3 or below) and also reported "worse than normal" sense of smell for weak odors (N = 35), and participants who scored below 24 on the Mini-Mental State Examination (MMSE; N = 106).

The main results of the first study are summarized: The mean proportion of correctly identified odors for men and women in the different age cohorts are displayed in Figure 1, showing that women perform better than men. This overall difference is statistically significant ($p < 0.0001$). The performance of women and men appears to converge at old age. However, when analyzing main effects of gender at each age cohort separately, women perform significantly better at all ages except for the oldest group (85-90). There was no significant interaction of gender by age. The overall gender difference was small in comparison to the variation within each gender: It had an effect size of about 0.2 standard deviations. A decrease in odor identification performance with increasing age was also obtained, but there was no significant interaction of gender and age.

Using hierarchal regression analyses, age, education, and gender were found to contribute to the variance in odor identification performance. When controlling for these demographic variables, cognitive speed and vocabulary (one of the three measures of semantic memory) had small but statistically significant influences on odor identification ability. Executive functioning was not related to odor identification performance. The demographic and cognitive factors included in this analysis together accounted for 17% of the total variance in odor identification.

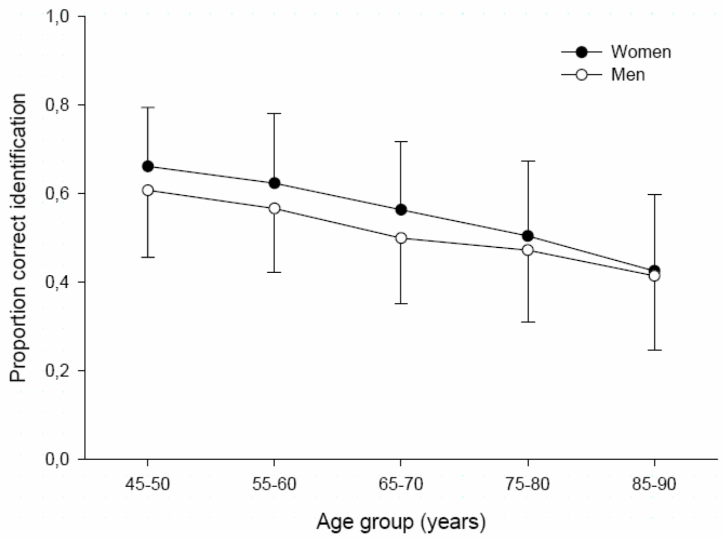

Figure 1. Mean proportion (± SD) of correctly identified odors as a function of gender and age.

Study 2: Gender differences in chemosensory perception and event-related potentials

For this study, 36 healthy, young participants (17 men and 19 women) were tested. Thirteen of the women took contraceptives, and the women were tested randomly with respect to the menstrual cycle. The odor stimuli were three concentrations of vaporized pyridine; 13%, 15%, and 19% of total air flow, each delivered 20 times to the participants. Every 30 s, a stimulus was injected for 200 ms in a constant airflow of 8 l/min to one of the participants' nostrils. Stimulus order was randomized (using four randomized stimulus lists, balanced across gender), and stimulated nostril was balanced across gender. Electrophysiological brain activity evoked by pyridine was measured during 1500 ms after stimulus onset. Participants rated each stimulus for perceived intensity, unpleasantness, and sensory irritation (which was explained to the participant as a stinging, smarting, pungent or dry sensation in the nose).

Results of the perceptual ratings are shown in Figure 2. Interaction effects of gender and stimulus concentration are found for all three perceptual aspects; women perceive the difference between stimulus concentrations as larger than men do. For intensity and unpleasantness, the overall ratings displayed a tendency of higher ratings by women than by men. When analyzing gender effects on intensity and unpleasantness for each stimulus concentration, the strongest concentration displayed significantly higher ratings by women than by men. The irritation rating showed no main effect of gender. As would be expected, all three perceptual aspects were influenced by the stimulus concentration. Higher concentrations were rated as more intense, more unpleasant, and more irritating.

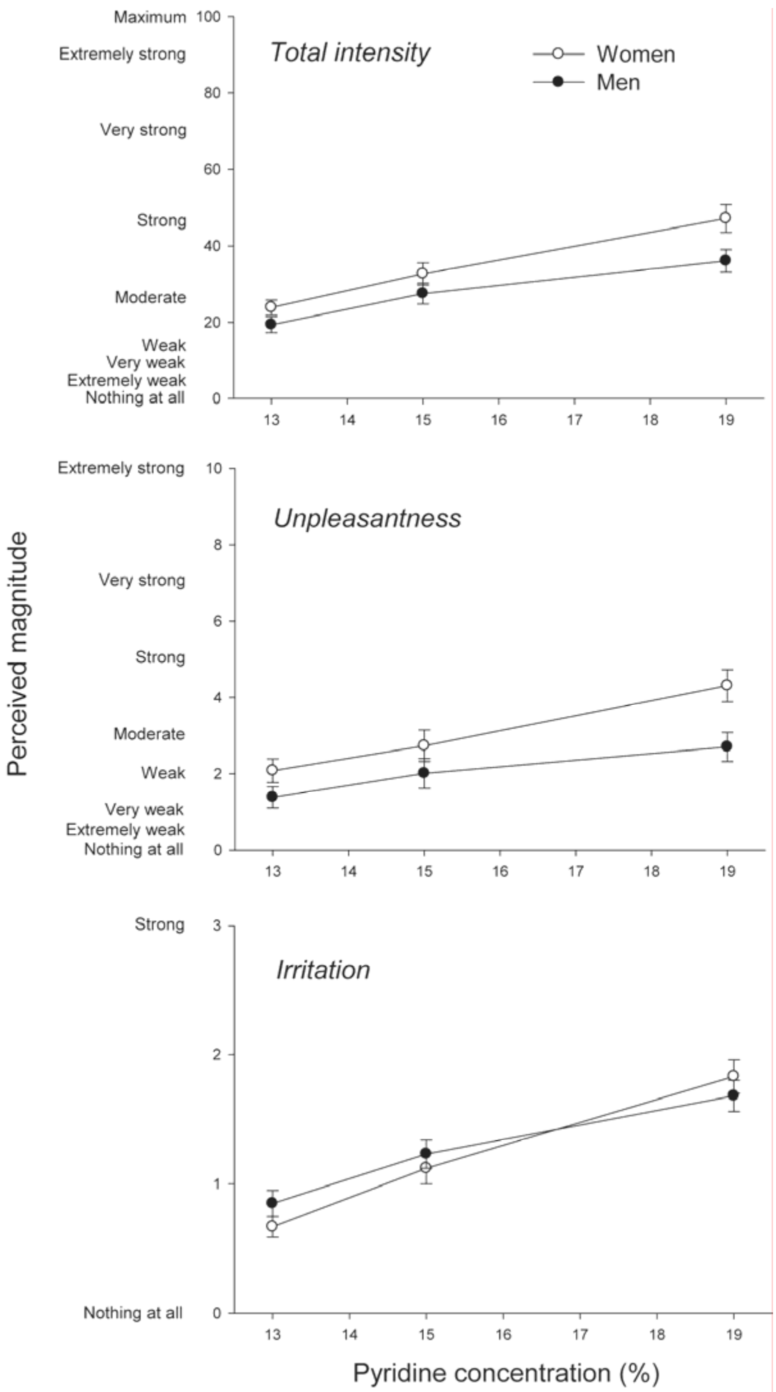

Figure 2. Mean ratings (± SE) of chemosensory perception in men and women.

These behavioural findings were corroborated by the findings of CSERP responses to these stimuli. Men's N1 component of the CSERP wave - occurring at about 350 ms after stimulus delivery - was more difficult to recognize from background noise, than was women's N1. The largest positive deflection, denoted P2/P3, occurred at about 500 ms, as shown in Figure 3. The P2/P3 was easily identified in both women and men. At higher stimulus concentrations, CSERP responses (N1 and P2/P3 amplitudes) increased, and the components' latencies decreased. Men displayed a significantly smaller P2/P3 than did women, as shown in Figure 4. This difference was independent of stimulus concentration. Women also displayed shorter P2/P3 latencies than men at the central electrode site (Cz).

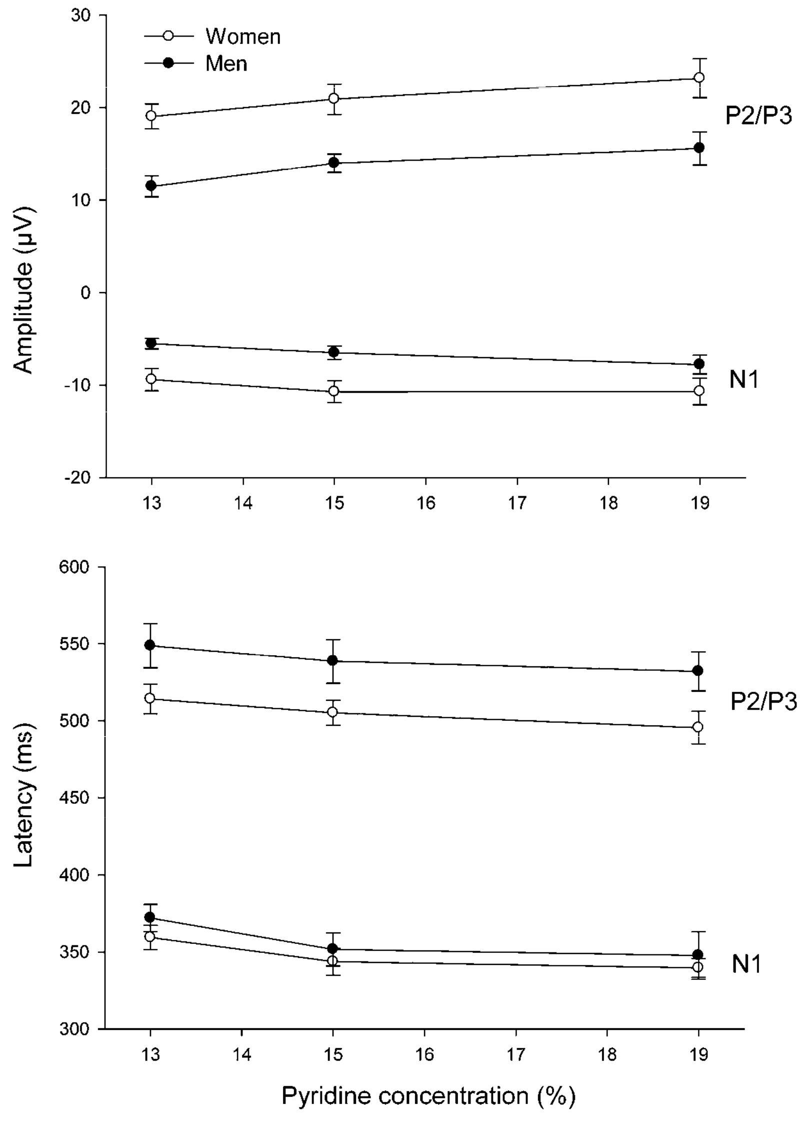

Figure 3. Mean (± SE) CSERP amplitudes and latencies in men and women.

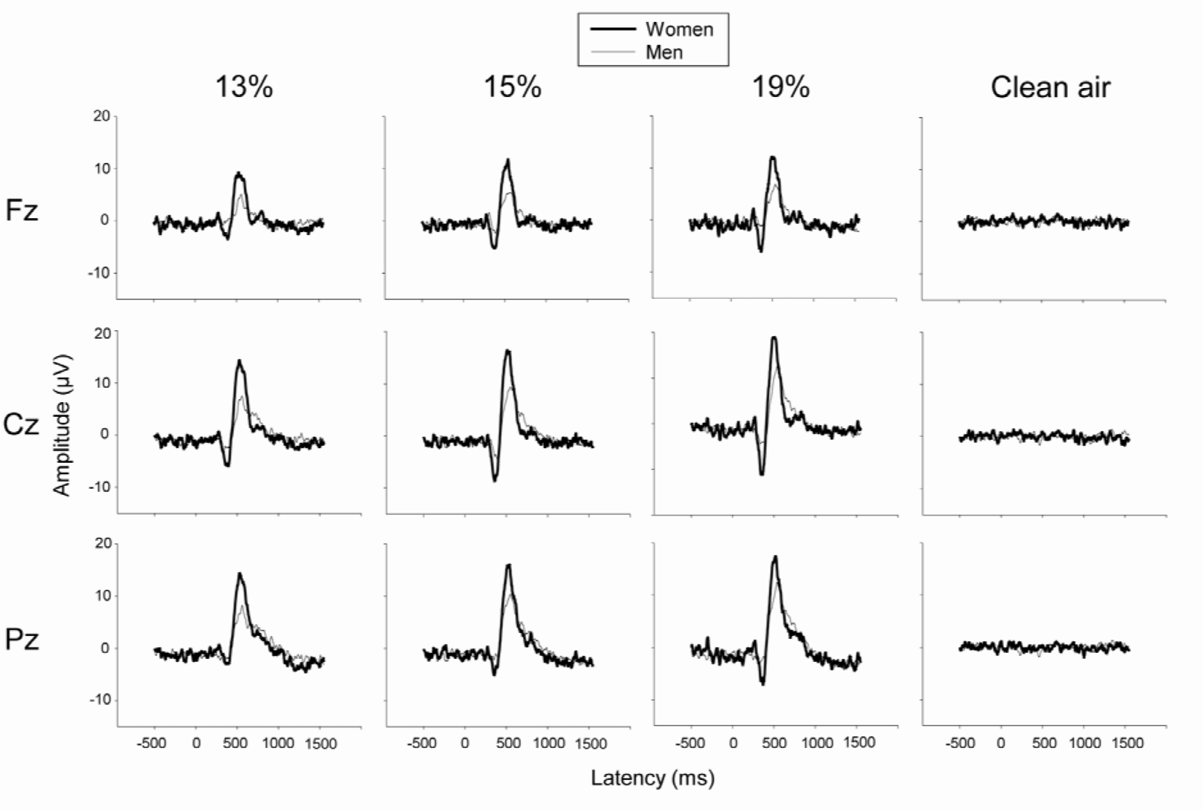

Figure 4. Group averages of CSERP responses to three concentrations of pyridine and clean air (control condition).

CONCLUSIONS AND GENERAL DISCUSSION

The two studies included in this work have assessed gender differences in behavioural and physiological aspects of olfactory functioning. In the first study, women showed significantly higher ability than men to identify odors from a list of four similar alternatives. This difference, albeit small, was present in all studied age cohorts, except from the oldest (85-90 yrs), where no gender difference was observed. However, there was no significant convergence of women's and men's odor identification ability in older age (i.e., no gender by age interaction). Notably, fewer participants were included in this oldest age cohort than in the younger age cohorts. At this advanced age, mortality rates might also bias the selection. The general interpretation of this result is that women show a small, but significant advantage over men in identifying odors, and that this difference is relatively constant across the adult lifespan. A general decline in odor identification was found at higher age. This has frequently been reported in previous studies (Doty et al., 1984b; Wysocki & Gilbert, 1989; Murphy et al., 2002). Some researchers have found earlier age-related decline in odor abilities in men than in women (Murphy et al., 2002; Doty et al., 1984; Ship et al., 1996; Wysocki & Gilbert, 1989). However, it should be noted that Wysocki and Gilbert (1989) showed this pattern for detection sensitivity and self-reported olfactory acuity, whereas odor identification performance varied greatly between odorants. The larger decline in men's odor identification ability at old age is not always found (Brämerson et al., 2004). It should be noted that our analyses are based on a population-based sample that is screened for cognitive impairment and severe olfactory impairment. Murphy and colleagues (Murphy et al., 2002) reported that severe olfactory impairment in older age occurs more often in men than in women. Further study with longitudinal data is necessary to investigate possible interactions of age and gender in odor identification ability.

The cognitive tests performed by the participants made it possible to investigate cognitive abilities that are needed for successful odor identification. Cognitive speed and vocabulary made significant contribution to odor identification performance when age and gender were controlled for. Vocabulary is an ability which is related to the odor identification task in that both tests require word knowledge (to produce synonyms, vs. to recognize the response alternatives). As previously noted, women often perform better than men in semantic/verbal tests. In this study, there was a very small advantage for women in letter fluency, but no gender difference in vocabulary or category fluency (as can be seen in Table 2 in Larsson et al., 2004). Notably, vocabulary was the only semantic/verbal test that contributed independently to variance in odor identification in the analyses. The role of cognitive speed in odor identification performance might consist of a more rapid evaluation of the response alternatives in comparison with a present odor. It has also been argued that age-related decreases in processing speed reflect general neurophysiological changes in the nervous system (Salthouse 2000). This can explain why speed measures contribute to age-related differences in various cognitive measures (Salthouse 1996).

In sum, the present results indicate that the gender-differences in odor identification ability are not caused entirely by female advantage in semantic/verbal ability and cognitive speed. Although variation in cognitive abilities could explain a statistically significant part of the olfactory identification ability, the largest part of the variation remains unexplained. This variation might be explained by a variation in olfactory sensitivity. The olfactory identification tests rely on sensory acuity. Low performance in identification is primarily regarded as a sign of olfactory loss (Nordin et al., 1998). In particular, detection sensitivity and quality discrimination is relevant for correctly identifying an odor (Cain & Gent, 1988; Cain & Potts, 1996; Dulay & Murphy, 2002). Using a principal component analysis of performance on various olfactory and non-olfactory tests, Doty and colleagues showed that odor identification (UPSIT) and detection sensitivity is caused by the same underlying component (Doty et al., 1994). In the first of the present studies, high demands were probably placed on discriminative processes, since the response alternatives were perceptually similar to the corresponding test odorant. A free (not cued) odor identification task would presumably show a larger influence of cognitive factors, as it poses higher cognitive demands (Larsson et al., 2000). Thus, the present results can be verified and extended by use of free odor identification tasks in the context of gender differences.

Other aspects of chemosensory perception (cortical responses and perceptual ratings) were addressed in the second study. Results show that women tended to rate the strongest, most irritating odor stimulus (19% pyridine) as more unpleasant and intensive than men did. This supports previous findings that chemosensory perception at supra-threshold levels evoked higher intensity and unpleasantness ratings in women than in men (Wysocki & Gilbert, 1989; Cometto-Muniz & Noriega, 1985), and extends these by showing that the observed gender difference in perceptual ratings of supra-threshold mixed olfactory/trigeminal stimuli is larger for higher stimulus intensities.

Gender differences in olfactory perception might start as early as about 350 ms after the odorant enters the nasal cavity: The N1 component of the CSERP is more identifiable in women than in men, due to a higher signal-to-noise ratio for this neural response. At the P2/P3 component, a gender difference is shown as significantly larger amplitudes in women than in men.

The gender difference in ERPs suggests a neurophysiological basis for a general gender differences in early olfactory and trigeminal perception: Chemosensory stimuli evoke a stronger representation in the brains of women. This difference is independent of olfactory/trigeminal properties of the stimulus. The results are in line with previous findings in olfactory ERPs (e.g., Becker et al., 1995) and olfactory fMRI (Yousem, Maldjian, Siddiqi, Hummel, Alsop, Geckle, et al., 1999; Savic, Berglund, Gulyas, & Roland, 2001), and are also supported by a recent study in trigeminal perception: Women show higher trigeminal CSERP responses than men for the pure irritant CO2 (Lundström, Frasnelli, Larsson, & Hummel, in press).

In particular, the insular region is of interest, since the anterior/central insula has been proposed as one of the generators of the CSERP (Kettenman et al., 1997). During odor stimulation in fMRI studies, the left anterior insula is activated (Royet, Plailly, Delon-Martin, Kareken, & Segebarth, 2003; Kareken, Mosnik, Doty, Dzemidzic, & Hutchins, 2003; Savic, Gulyas, Larsson, & Roland, 2000) Interestingly, this region is more activated when subjects are performing an odor intensity discrimination task, or an odor quality discrimination task, than when just smelling the odor (Savic et al., 2000), and it is also more activated when participants try to identify an odor (Kareken et al., 2003). Thus, it can be regarded as a region that is engaged in both basal perception and evaluation of odor stimuli. This region has shown more hemodynamic activity in women than in men during odor stimulation (Yousem et al., 1999), although the findings are not conclusive (Royet et al., 2003). Bengtsson and colleagues (Bengtsson, Berglund, Gulyas, Cohen, & Savic, 2001) speculated that the insular region, along with the caudate nucleus, might be a neurophysiological basis for female superiority in olfactory discrimination. Women's stronger neural representation of chemosensory stimuli might be reflected in the ratings of intensity, unpleasantness, and irritation (i.e., trigeminal activation). This stronger neurophysiological response in women might also play a role in odor identification.

It can be suggested from the present results that the evaluation of the sensation evoked by the stimulus is not directly reflected in the CSERP parameters: They do not display the interaction between gender and stimulus concentration that was a constant feature of the perceptual ratings. Possibly, the ratings of these unpleasant, irritating stimuli are also influenced by an evaluation of the physiological arousal caused by the stimulus, which is not captured by ERP recordings (Chapman, Donaldson, Nakamura, Jacobson, Bradshaw, & Gavrin, 2002). A possible causal role of ERPs in chemosensory perception has not yet been proposed. To address this issue, further studies should use a wide range of chemosensory stimulus concentrations, and combine CSERP recordings with other physiological measures such as galvanic skin response, to approach the causal mechanisms underlying perceptual reports of e.g. intensity, unpleasantness and irritiation.

The present finding of slightly faster chemosensory processing in women than in men was recently supported in the study by Lundström and colleagues (Lundström et al., 2005), who used the pure trigeminal stimulus CO2. Although the gender difference in chemosensory processing speed has not yet been convincingly explained, slower processing speed (longer latencies) and less neural activity (smaller amplitudes) often occur together, for example in aged populations (Geisler et al., 1999; Evans et al., 1995; Murphy et al., 2000). Thus, the present results suggest that neural processing speed and amount of neural resources allocated to the chemosensory stimulus might be two related measures, even in healthy young participants.

In the context of gender differences in CSERPs, further studies can investigate to what extent the difference in CSERP amplitude depends on cognitive factors, such as allocation of attention to the incoming stimulus, and to what extent it is caused by a difference in peripheral sensitivity of men and women. General attentional influences on gender differences can be performed by contrasting an "attend" condition (participants respond to stimulus by button-pressing) with an "ignore" condition (participants are occupied with a task unrelated to the stimuli) during CSERP recordings. The evaluation of changes in stimulus level might also influence CSERPs differently in men and women. This possibility can be investigated by contrasting CSERPs evoked by a monotonous stimulation (same concentration every time) with a CSERP evoked by the same stimulus concentration in a context of weaker and stronger stimulus concentrations. Dalton and colleagues (Dalton, Doolittle, & Breslin, 2002) found that women in reproductive ages can significantly lower their olfactory detection threshold across repeated test exposures. Men, in contrast, do not show any change across repeated exposures. The functional mechanisms underlying these results are not well understood. Given that the CSERP amplitudes and latencies depend on detection thresholds, they should change in women, but not in men, across several recording sessions. It might also be of interest to investigate how the present gender differences in CSERPs changes during the cause of one experimental session (i.e., sensitization/habituation effects).

Due to the history of gender-bias in science, and the possible socio-political consequences of gender differences in psychological abilities, gender differences are constantly debated (e.g., Crawford & Chaffin, 1997; Hyde & Linn, 1988). The controversy of studies on gender differences is perhaps not generated by the empirical findings per se, but rather by the explanation of the results to e.g. evolutionary mechanisms (suggesting genetic influences) or acquired abilities (attributing differences in performance to e.g. gender-stereotypical patterns of experience and learning). Thus, researchers should be cautious regarding causal factors of gender differences. It should be emphasized that gender is a subject variable. Gender differences are assigned by quasi-experimental procedures, which have lower methodological status than that of an experimental design, in which assignment of independent variables is randomized (Shadish, Cook, & Campbell, 2002). A methodological problem in research on gender differences is the large number of variables that are associated with gender: Men and women differ in biological parameters (e.g., hormonal levels), but also in environmental factors (e.g., gender roles and experiences). Complex interactions between several factors make it difficult to establish the causes of gender differences. Environmental factors have been shown to influence olfactory acuity: e.g. factory workers, typically a male profession, more frequently display olfactory loss than do workers in other environments. According to self-reports, the causes of work-related olfactory loss are chemical exposure and head injury, and male factory workers appear to be more susceptible to these environmental effects than female factory workers (Corwin, Loury, & Gilbert, 1989). A study which emphasizes the role of environmental factors in odor identification is Murphy and Cain's (1986) investigation of blind people's ability to detect odors and to identify odors without cues. They found that the blind performed worse than sighted controls in odor detection sensitivity, but better in odor identification. The better odor identification performance in the blind is presumably due to more accumulated knowledge about odors. Cain and colleagues (Cain, Stevens, Nickou, Giles, Johnston, & Garcia-Medina, 1995) reported that young children are as sensitive as young adults in their sense of smell, but they lack odor-specific knowledge that is necessary for identifying odors. Applying these arguments to the present findings of gender differences, the lower performance in odor identification in men might be due to less general experience with odorants. This would imply that e.g. "stereotypically male" odors (e.g., motor oil) are more easily identified by men than by women, and that women are better at identifying "stereotypically female" odors (e.g., nail polish remover). Participants in an experiment by Cain (1982) predicted such results. However, in a follow-up experiment with a second group of participants, women were better than men in identifying odors, independent of stereotypes (Cain, 1982).

Environmental causes of group differences on a trait should reasonably make the groups diverge as more group-specific experience is accumulated during life. This is probably the case for some gender differences in psychological abilities (Crawford & Chaffin, 1997). As Hama (2004) points out, however, differences between women and men in psychological abilities are sometimes observed in young children, before gender roles reasonably exert major influences. This seems to be the case in the olfactory domain. Doty (1997) have reported that odor identification abilities of girls and boys show a women's advantage in the youngest group tested (5-9 yrs.) as well as the oldest group (over 60 yrs.), suggesting that e.g. acquired knowledge of odors through experiences during lifetime are not a main cause of the gender difference in odor identification ability. Studies by Richman and colleagues (Richman, Wallace, & Sheehe, 1995; Richman, Post, Sheehe, & Wright, 1992) show the same pattern for children from around four years of age. In a study by Makin and Porter (1989), female-gendered newborns preferentially turned their head towards a gauze pad impregnated with the breast odor of a feeding mother, compared to a non-odorous gauze, whereas male-gendered newborns did not show any preference. Doty and colleagues (Doty, Applebaum, Zusho, & Settle, 1985) have investigated gender differences in olfaction across cultures. Their results revealed the same pattern of better performance in women, in both a Japanese group and three ethnic groups living in the USA.

Researchers claiming an influence of gender-specific biological variables (such as gonadal steroids) on reported gender differences in perceptual function can get indirect support from studies of females using repeated assessment at different phases of the menstrual cycle. This methodology has been applied to auditory sensitivity (see review by McFadden, 1998) and auditory ERPs (Walpurger, Pietrowsky, Kirschbaum, & Wolf, 2004), giving evidence for the view that perceptual function changes during the menstrual cycle. The olfactory sensitivity in women, as well as the auditory sensitivity, seems to vary in a similar manner across the menstrual cycle, peaking during at ovulation phase (Doty, 1986). One CSERP study has supported this conclusion (Pause et al., 1996). Although influences of circulating gonadal hormones (e.g., estrogen and progesterone) might be a cause for gender differences in olfactory sensitivity, for several odorants tested, gender differences are not limited to the reproductive ages (Koelega & Köster, 1974). The direct influence of gonadal hormones on olfaction has been questioned, since contraceptives do not change the pattern of olfactory sensitivity fluctuations across the menstrual cycle (Doty, 1986). The relation between neuroendocrine factors and the olfactory system are complex, and not fully understood.

The evolutionary causes of the gender differences in chemosensory function are not known. It has been speculated that gender-differentiated survival strategies and reproductive strategies have resulted in better olfactory abilities in women (see Brand & Millot, 2001). However, before the evolutionary mechanisms of gender differences in chemosensory abilities can be understood, further basic research is needed concerning its development and physiological basis. Studies of chemosensory abilities in young children, and studies using longitudinal designs, are particularly warranted. Research strategies to adequately assess biological gender differences are discussed by Becker and colleagues (Becker, Arnold, Berkley, Blaustein, Eckel, Hampson, et al., 2005), and in the peer comments following the review by Dao and Leresche (2000; see also Halpern, 1997 for a critical discussion on the "nature/nurture" conceptualization).

Although the biological basis of perceptual gender differences can be difficult to assess, this topic is receiving increased attention from within the basic and clinical science communities, since it is assumed to account for marked differences in disease incidence, manifestation, prognosis, and treatment observed between the sexes (Becker et al., 2005; Dao and LeResche, 2000). Women are more likely to suffer from clinical pain syndromes such as migraine and fibromyalgia (reviewed by Fillingim, 2000), and women report more severe clinical pain symptoms, particularly in the orofacial region (Dao & LeResche, 2000). Since these clinical reports are in line with experimental studies on pain perception, it has been suggested that the observed gender differences are generated by differences in the way painful stimuli are processed by the central nervous system (Dao & LeResche, 2000). The present results from perceptual ratings and CSERPs support this view. Understanding the nature and magnitude of gender differences in chemosensory function is thus important from a clinical viewpoint. Women display a higher prevalence than men in reporting odor-related environmental complaints, such as sick-building syndrome and chemosensory intolerance. Symptoms categorized as chemical sensitivity are reported by women in about 80% of the cases (Fiedler & Kiepen, 1997). The present results suggest further clinical investigations of ERPs evoked by olfactory and trigeminal stimuli. Especially chemical irritants, which evoke painful sensations in the nose, might become useful in ERP investigations in clinical populations (Hummel, 2000). Although our first study on the CSERP as a means to evaluate chemical hypersensitivity did not show differences between gender-matched hypersensitive and insensitive groups (Nordin, Martinkauppi, Olofsson, Hummel, Millqvist, & Bende, 2005), higher vulnerability to chemosensory-related distress is likely to have a physiological basis. In contrast, men's less proficient smelling abilities makes them more vulnerable to olfactory impairment due to environmental factors, which can influence both physical and psychological health negatively. Thus, careful and thorough assessments of the gender differences in the chemical senses might provide knowledge that is important for a variety of topics in the life sciences.

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