Subjects with Congenital Anosmia Have Larger Peripheral but Similar Central Trigeminal Responses

Most odorants not only stimulate olfactory receptor neurons but also activate the intranasal trigeminal nerve. The simultaneous activation of the olfactory and the trigeminal system leads to an interaction in the brain. Therefore, assessment of the trigeminal impact of odorants may be difficult in subjects with a normal sense of smell. To obtain a deeper insight into both, mechanisms of changes in trigeminal sensitivity in anosmic patients and interactions between the olfactory/trigeminal systems in healthy subjects, 21 patients with isolated congenital anosmia (ICA) were investigated in this series of explorative, hypothesis-generating experiments and compared with 35 healthy controls. Trigeminal sensitivity was measured by psychophysical (lateralization task, intensity ratings) and electrophysiological (trigeminal event-related potential, negative mucosal potential) means. ICA patients were found to have higher peripheral activation than controls. On central levels, however, similar responsiveness to trigeminal stimuli was found in ICA patients when compared with healthy subjects. The results of the study are discussed by proposing a model of mixed sensory adaptation/compensation in the interactions between olfactory and the trigeminal system.

Keywords: anosmia, ERP, NMP, patients

Introduction

Most odorants not only stimulate olfactory receptor neurons but also activate the intranasal trigeminal nerve (Doty and others 1978). During the last years, a number of trigeminal chemoreceptors have been identified, which are activated by different chemicals (e.g., Waldmann and others 1997; Caterina and Julius 1999; McKemy and others 2002; Jordt and others 2004). Thus, not only the olfactory but also the trigeminal system encodes information related to the quality of an odor that seems to contribute significantly to the perception of odors (Laska and others 1997).

The simultaneous activation of the olfactory and the trigeminal system leads to an interaction in the brain: it had been shown that trigeminal stimulation can modulate olfactory sensations (Cain and Murphy 1980; Livermore and others 1992). Olfactory stimuli, on the other hand, have been shown to alter trigeminal sensations producing either amplification (Kobal and Hummel 1988) or inhibition of the response (Cain and Murphy 1980; Livermore and others 1992).

Therefore, assessment of the trigeminal impact of odorants may be difficult in subjects with a normal sense of smell. This is the reason why anosmic patients are frequently investigated to estimate the trigeminal impact of odorants. However, another problem arises in this experimental approach: loss of olfactory function leads to a reduced intranasal trigeminal sensitivity. Anosmic patients were found to have smaller amplitudes of trigeminal event-related potentials (tERPs) when compared with healthy controls (Hummel and others 1996a). In addition, they were found to have higher trigeminal thresholds on behavioral measures than healthy controls (Walker and others 2001). Independent from the pathogenesis of the olfactory disorder (upper respiratory tract infection [URTI], posttraumatic, idiopathic), anosmic and hyposmic patients had fewer correct answers in a lateralization task, a test of trigeminal function based on the fact that trigeminal activation is a prerequisite for correct localization of monorhinally presented stimuli (Hummel and others 2003). Finally, anosmic patients had higher thresholds on a detection test for formic acid when compared with healthy controls. Again, this was independent from the history of anosmia: both patients being anosmic after a trauma and patients anosmic due to sinususal disease were found to have a decreased trigeminal sensitivity (Gudziol and others 2001). Thus, it seems that patients with anosmia additionally have a reduced trigeminal sensitivity, which is non-specific, that is, independent from the pathogenesis of the anosmia.

It is unclear whether the reduced trigeminal function of patients with olfactory disorders is 1) a direct consequence of the event causing the olfactory disorder (e.g., head trauma, URTI) itself or 2) independent from this triggered by a reduced sense of smell. In other words, it is not clear if the incidence that damaged the olfactory tissue also directly harms structures involved in the perception of intranasal trigeminal chemosensory sensations. Alternatively, structures involved in the perception of intranasal trigeminal chemosensory sensations for full sensibility may rely on a functioning olfactory pathway.

In the second scenario, it would be interesting to detect the anatomical level at which the olfactory and the trigeminal system interact. In fact, it has been shown that the olfactory and the intranasal trigeminal system interact on central levels. So, interference between both systems can be found when applying mixed olfactory/trigeminal stimuli in healthy subjects. Information from the olfactory system modulates intensity as a measure of the trigeminal system (Cain and Murphy 1980; Kobal and Hummel 1988). As the effect was also found when stimuli were presented birhinally, it was concluded that interactions between the 2 systems occur in the central nervous system (Cain and Murphy 1980). This was corroborated by electrophysiological recordings. The olfactory/trigeminal interaction was found to affect mainly late event-related potential (ERP) components (Livermore and others 1992), which are thought to reflect the interaction between the subject and the stimulus (Coles and Rugg 1995; Pause and others 1996).

It is possible to explore the relationship between the olfactory and the intranasal trigeminal system by investigating...
patients who never have had a sense of smell, that is, patients with congenital anosmia. Up to 5% of the normal population is anosmic, although in many cases they are not aware of it (Bramson and others 2004). Approximately, 1% of these are born without a sense of smell; therefore they are called congenitally anosmic (Jafek and others 1990; Leopold and others 1992). Although it can be associated with other deficits (e.g., Kallmann’s syndrome), in most cases congenital anosmia is an isolated deficit (isolated congenital anosmia [ICA]) (Jafek and others 1990; Leopold and others 1992).

Thus, to obtain a deeper insight into both mechanisms in olfactory loss and interactions between olfactory/trigeminal systems in healthy subjects, in this series of explorative, hypothesis-generating experiments, patients with ICA (Jafek and others 1990; Leopold and others 1992) were investigated and compared with healthy controls with regard to measures of trigeminal sensitivity on different levels of perception.

The whole study was conducted according to the Declaration of Helsinki on biomedical research involving human subjects and it was approved by the local ethics committee. During enrollment, subjects were given detailed information about all testing procedures. Written consent was obtained from all subjects prior to the study.

**Experiment 1: Assessment of Olfactory Function and Lateralization Task**

**Materials and Methods**

In the clinic where the study was performed, 90% of the patients with ICA are female. Thus, only women were included in the study in order to avoid gender effects. A total of 21 ICA patients were included. Twelve of them were between 18 and 35 years old, 9 were older than 50 years. Congenital anosmia was diagnosed based on the following criteria: medical history (patients indicated not to remember to ever have smelled anything; patients indicated no major head trauma in their childhood), psychophysical examination (results in a test of olfactory function indicative of functional anosmia; no reports on olfactory sensations during the olfactory test) (Kobal and others 2000), electro-physiological measurements (no response in the measurements of olfactory ERPs to hydrogen sulfide) (Kobal and Hummel 1998), and magnetic resonance imaging (aplasia/hypoplasia of olfactory bulb/tract detectable and flattened olfactory sulcus) (Yousen and others 1996; Abolmaali and others 2002). Apart from anosmia, all participants were in an excellent state of health, as revealed also by a detailed ear, nose, and throat (ENT) examination.

Their results were compared with those obtained in 35 healthy subjects. Nineteen of them were between 18 and 35 years of age, 16 were older than 50 years. To ascertain normal olfactory function, the subjects underwent an olfactory test, an ENT examination, and a detailed medical history. Patients and controls were not different with regard to age (mean age of patients: 40 years; mean age of controls: 40 years; $P > 0.05$).

Olfactory function was assessed using the “Sniffin’ Sticks” olfactory test kit (Hummel and others 1997; Kobal and others 2000) (Burghart, Wedel, Germany), where odors are presented in commercially available felt-tip pens. The kit consists of separate tests for phenylethyl alcohol odor thresholds, odor discrimination, and identification. Results of the 3 subtests are presented as a composite threshold-discrimination-identification (TDI score.) Based on a multicentre investigation, subjects with a TDI score below 16 are considered functionally anosmic, with a score between 16 and 31 patients are considered hyposmic, and with a score equal to/above 31 patients are identified as normosmic (Kobal and others 2000).

Trigeminal activation was quantified by the subjects’/patients’ ability to lateralize stimuli presented to either the left or the right nostril (Lateralization task). Based on previous studies, pure (99%) eucalyptol (Aldrich-Chemie, Steinheim, Germany) was used for the odor localization paradigm (Doty and others 1978; Berg and others 1998; Hummel and others 2003). The odor was presented to either one nostril in a high-density polyethylene squeeze bottle (total volume 250 ml) filled with 30 ml of the odorant or the other nostril in an identical bottle filled with 30 ml of odorless propylene glycol. The bottles had a pop-up spout that was placed into either nostril. A puff of approximately 15 ml air was delivered by pressing the 2 bottles at the same time by means of a hand-held squeezing device. The subjects were held onto the spouts to prevent their movements inside the nostril, which accompanied squeezing of the bottles; movement of the spouts might produce mechanical irritation, which, in turn, might interfere with the subject’s ability to localize the odor. A total of 40 stimulants were applied to the blindfolded subjects/patients at an interstimulus interval (ISI) of approximately 40 s; stimulation of the left or right nostril followed a pseudorandomized counterbalanced sequence. After each stimulus, subjects/patients were asked to identify the nostrile where the odorant had been presented. The sum of correct identifications was used for further statistical analyses (Berg and others 1998; Hummel and others 2003). Testing required approximately 30 min.

Statistical analyses were performed using a statistical package for the social sciences (SPSS) 12.0 (SPSS Inc., Chicago, IL). Repeated measures analysis of variance was computed with variables of interest (between-subject factors “age group” [young, old], and “status” [patient, control]; within-subject factors where applicable). For post hoc analyses, $t$ tests were calculated. The alpha level was set at 0.05. Means are indicated together with standard errors of means (SEMs) in brackets.

**Results**

With regard to the lateralization task, older subjects had significantly lower scores when compared with younger subjects, indicating lower sensitivity (“age group”; $F_{1,50} = 12.7, P = 0.001$). However, no significant effect of the factor “status” could be observed (young patients: 37.3 [0.6], young healthy controls: 38.6 [0.5], old patients: 32.1 [2.5], old healthy controls: 34.7 [1.4]) (Fig. 1).

**Discussion**

In this first experiment, ICA patients were found to have a similar ability to lateralize odorous stimuli compared with healthy controls. This is unlike the results in patients with acquired anosmia (AA), which were found to have lower scores than healthy subjects (Hummel and others 2003). Although the same technique was applied in the previous study, all groups—including the control group—had higher scores in the present study. It might be that differences between patients and control were not significant because the task was too simple. Maybe the used stimulant led to higher trigeminal activation in the present study leading to a ceiling effect and making it thus impossible to separate between patients and controls.

![Figure 1](https://academic.oup.com/cercor/article-abstract/17/2/370/317620)
However, earlier studies showed the results of the lateralization task to be correlated significantly to the duration of olfactory dysfunction (Hummel and others 2003). The longer the olfactory dysfunction lasted, the higher the patients scored in the lateralization task. Therefore, it seems as in the case of a permanent anosmia, trigeminal sensitivity recovers over time, with an unclear endpoint.

In the following experiment, tERPs were recorded. They are a means to investigate trigeminal activation on a central level, as ERPs are electroencephalography-related responses generated in the cortex. The generation of tERP is thought to be mainly caused by the activation of A-fibers (Handwerker and Kobal 1993). tERPs are routinely used in pain research to investigate effects of antinociceptive drugs (Kobal and others 1990; Hummel and others 1994; Lotsch and others 1997). Their early components are mainly dependent on stimulus characteristics (exogenous components), whereas the later components are mainly a reflection of the interaction between the subject and the stimulus (endogenous components) (Pause and Krauel 2000).

**Experiment 2: ERP Measurements and Intensity Ratings**

**Materials and Methods**

The same participants as in Experiment 1 were tested in this experiment. The same statistical procedures were applied. tERPs were recorded in response to CO2 stimuli of 40%, 50%, and 60% v/v. Stimulation duration was 200 ms. Each stimulus concentration was presented 15 times. The ISI was 30 s. This resulted in a duration of the session of approximately 25 min. Stimuli were presented to one nostril. Subjects were seated comfortably in an air-conditioned room. They received white noise through headphones to mask the switching clicks of the stimulation device. To stabilize vigilance, subjects performed a simple tracking task on a computer screen. Using a joystick, they had to keep a small square inside a larger one, which moved unpredictably (Hummel and Kobal 2002). tERPs were recorded at position Cz of the international 10-20 system. Eye blinks were monitored via the Fp2 lead. tERPs were reference against linked earlobes (A1, A2). The sampling frequency was 250 Hz, and the pretrigger period was 500 ms with a recording time of 2048 ms per record (bandpass 0.02-30 Hz). Recordings were filtered additionally off-line (low pass, 15 Hz). After records contaminated through motor artifacts or blink artifacts had been discarded, the ERP was averaged and analyzed for amplitudes and latencies of the major peaks N1 and P2.

After each stimulus presentation during the tERP session, subjects rated stimulus intensity on a visual analog scale displayed on the computer screen. Using a joystick, subjects moved a marker on the scale. The right end of the scale indicated an "extremely strong" intensity (100%); the left end indicated that no stimulus had been perceived (0%) (Hummel and Kobal 2002). Data for each stimulus condition were averaged to obtain a mean rating.

**Results**

No significant difference could be observed in latencies and amplitudes of tERP between patients and healthy controls. With regard to age effects, older subjects had smaller ERP amplitudes P3 and longer latencies of N1 ("age group": F1,48 = 7.6, P < 0.01) when compared with younger ones. In addition, there was an effect of stimulus concentration on ERP parameters, with higher amplitudes and shorter latencies of responses to stimuli of higher concentrations ("concentration": F2,76 = 3.8, P < 0.026; Fig. 2).

With regard to intensity ratings, patients rated stimuli as less intense when compared with healthy controls ("status": F1,47 = 4.06, P = 0.049). In addition, older subjects rated stimuli as less intense when compared with younger ones ("age group": F1,47 = 5.66, P = 0.008). As expected, stronger stimuli elicited higher intensity ratings ("concentration": F2,94 = 205.6, P < 0.001).

**Discussion**

ICA patients were found to rate CO2 stimuli as weaker when compared with healthy controls. This is in line with a number of other studies showing that anosmic patients compared with controls have a lower trigeminal sensitivity when considering intensity ratings (Kendal-Reed and others 1998; Walker and others 2001). However, similar to Experiment 1, no significant difference between ICA patients and healthy controls could be detected with regard to the tERP measurements. In contrast, previous studies found early tERP components to be reduced in patients with AA. Early ERP components are known to be exogenous factors, for example, stimulus concentration or stimulus quality, and also to utilization time at the receptor (Pause and Krauel 2000; Frasnelli and others 2003).

In order to explore differences between ICA patients and controls on a peripheral level, measurements of the negative mucosal potential (NMP) were performed. It is a reflection of trigeminal activation at the level of the respiratory epithelium (Kobal 1985; Thurauf and others 1991, 1993; Lötsch and others 1997; Frasnelli and Hummel 2003). NMP is recorded from the nasal respiratory epithelium in response to chemical stimuli that produce sensations such as tickling, stinging, or burning (Hummel and others 1991; Laska and others 1997). Evidence from studies in animals (Thurauf and others 1991) and humans (Thurauf and others 1993) indicates that its signal generation is not related to autonomic reflexes. Measurement of the NMP has also been shown to be sensitive to peripheral effects of analgesics (Kobal 1985; Lötsch and others 1997).

The NMP is thought to be the result of summating receptor potentials of chemosensitive nociceptors of the trigeminal nerve (Thurauf and others 1993). It has been shown to be a result of activation of both C-fibers and Aδ-fibers (Hummel and others 1996b). In addition, the NMP is correlated to pain intensity ratings (Kobal 1985; Thurauf and others 1993; Hummel and others 1996b).

**Experiment 3: NMP Measurements**

**Materials and Methods**

The same subjects as in the previous experiments were tested. The same statistical procedures were applied.

NMPs were recorded from the same nostril as in Experiment 2 by means of tubular electrodes (polytetrafluoroethylene [PTFE] tubing filled with 1% Ringer agar containing a silver-chlorided silver wire) (Ottoson 1956). Placement of the electrode was controlled by nasal endoscopy (Leopold and others 2000). For reference, a silver-chlorided silver electrode was attached to the bridge of the nose. The recording sites were selected according to accessibility, low signal-to-noise ratio, and/or absence of stimulus-induced artifacts (Hummel and others 1996b). To keep the electrode in place, it was attached to clips mounted on a frame similar to lensless glasses.

In order to test whether at a given position an NMP could be recorded or not, CO2 stimuli of 500 ms duration and 60% v/v were applied after placing the electrode on the mucosa. Criteria for a reliable NMP were 1) response of the typical shape within the time range of NMP (Kobal 1985) and 2) reproducible responses through 3 consecutive stimuli. If no reliable NMP could be recorded, the procedure was repeated up to 6 times. If still no reliable NMP could be recorded, the procedure was repeated for another day. If no NMP could be recorded on the second day, the measurements were considered as "no reliable NMP recordable.

Subjects received CO2 stimuli of 500 ms duration and concentrations of 40%, 50%, and 60% v/v. The ISI was 40 s. Stimuli were presented to a randomly selected nostril by means of a computer-controlled air dilution olfactometer 68 (Burghart, Wedel, Germany). This stimulator allows for application of rectangular-shaped chemical stimuli. Mechanical stimulation is avoided by embedding these stimuli in a constant flow of odorless, humidified air of controlled temperature (80% relative humidity; total flow: 8 L/min; 36°C) (Kobal 1981).

Recordings were made with a direct current (DC) amplifier (low pass 30 Hz; Toennis, Germany). After analog-to-digital conversion (sampling rate 62.5 Hz), records of 8192 ms were obtained. The pretrigger period was 500 ms. Using a video system, subjects were monitored for movements during the recording periods. Records that might have been contaminated by movements were excluded from further analysis. After averaging, the amplitude and latency of the negativity (peak N1) were measured.
Results

The NMP could successfully be recorded in 16 of the 19 healthy young controls (84%) and in 7 of the 12 young patients (58%). This percentage was smaller in older subjects: in 8 of 16 healthy old subjects (50%) and 4 of 9 old patients (44%) the NMP could be recorded. However, the difference between these numbers was not statistically significant (chi-square test: $P > 0.05$).

No group difference could be detected in NMP recordings. However, there was an effect of "concentration," with stronger stimuli eliciting larger amplitudes ("concentration": $F_{2,62} = 12.5, P < 0.001$). In addition, there was a significant interaction between "concentration" and "status" for NMP amplitude: no major difference could be detected in the response to the weakest stimulus (patients: 60 [32] µV, healthy controls: 50 [11] µV), whereas the response to the strongest stimulus was, on average, twice as large in the patients’ group compared with healthy controls (patients: 232 [70] µV, controls: 120 [23] µV, concentration by status: $F_{2,62} = 3.51; P = 0.038$) (Fig. 3).

Discussion

Stimulus delivery parameters were optimized for NMP and ERP paradigms, respectively. In the tERP measurements, both stimulus duration (tERP: 200 ms, NMP: 500 ms) and the ISI were shorter (tERP: 30 s, NMP: 40 s). These parameters were chosen because they have been shown to be optimal stimuli for the respective measurements (Hummel and Kobal 2002; Frasnelli and Hummel 2003, 2004). However, as tERP mainly depends on stimulus onset and stimulus concentration (Frasnelli and Hummel 2004), the differences in stimulus characteristics are not expected to cause a major bias in the results.

On a peripheral level, ICA patients had larger responses to strong trigeminal stimuli when compared with healthy controls. Healthy subjects exhibited smaller peripheral responses following CO2 stimuli of 50% and 60% v/v but not following 40% v/v. It has been reported that the CO2 threshold concentration (stimulus duration 500 ms) for recording an NMP is approximately 43% v/v (Thurauf and others 2002). Therefore, it may be that the weakest concentration, in some subjects, was below NMP threshold or led to a response in the range of the background noise, making it thus difficult to detect a group difference at that level. However, when compared with ICA patients, healthy subjects had smaller responses to stimuli that were clearly above this NMP threshold.

General Discussion

ICA patients were found to have larger peripheral electrophysiological responses. On central levels (tERP) and with the lateralization task, no significant differences to healthy controls could be detected. In contrast to the NMP findings, ICA patients rated CO2 stimuli as less intense when compared with healthy controls.

The results of the present study can be compared with previous ones—with the exception of the NMP, which to our
knowledge, has not been used in the assessment of trigeminal sensitivity in anosmic patients.

The enlarged NMP amplitudes of ICA patients indicate a higher peripheral susceptibility in ICA patients. The physioanatomical correlate of this is not clear and speculative. Higher susceptibility could be caused either by a higher density of trigeminal nerve endings or by a higher responsiveness of the existing nerve endings.

First, the higher peripheral responsiveness could be caused by a higher density of trigeminal nerve endings in the nasal mucosa. It has been shown in rats that some trigeminal ganglion cells with sensory endings in the nasal epithelium also have branches reaching directly into the olfactory bulb. The function of these branches and the direction of information transfer in the bulbar branch are not yet clear (Schaefer and others 2002). Although it has not been shown, it is possible that such collaterals are present also in the human olfactory bulb. ICA patients, however, have an aplastic or hypoplastic olfactory bulb (Abolmaali and others 2002). Thus, it is unclear where the trigeminal collaterals mentioned above end in the case of ICA patients. It is possible that they add to the overall number of free trigeminal nerve endings within the nasal mucosa, leading to a higher number of endings and, thus, to a higher peripheral responsiveness. In this scenario, no increased peripheral responsiveness should be found in AA patients.

The NMP findings of the present study could also be explained differently. The intrabulbar collaterals could transfer information from the olfactory bulb to the trigeminal system in healthy controls. It has been shown that ongoing stimulation of the trigeminal system results in adaptation and lower

Figure 3. (A) Grand means of NMP following stimuli of 60% v/v CO₂. Graphs are displayed separately for young subjects (left) and old subjects (right). Results for healthy subjects are indicated in black, results of patients are indicated in light gray. The black bar indicates the onset and duration of the CO₂ stimulus. (B) Amplitudes (means, SEM) of NMP following stimuli with 40%, 50%, and 60% v/v CO₂: results are displayed separately for younger healthy subjects, younger patients with ICA, older healthy subjects, and older ICA patients.
susceptibility. This has been shown even on peripheral levels using the NMP (Hummel and others 1996b). Therefore it could be speculated that the continuous excitation of olfactory structures in the daily life of healthy controls leads to an adaptation of trigeminal structures via these collaterals. If this hypothesis applies, peripheral responses should be increased also in AA patients. Thus, further studies in AA patients are needed to test if (1.) an increase in peripheral susceptibility is also found in the case of an olfactory loss in acquired anosmia, and if (2.) a regeneration of olfactory function would have the opposite effect.

The relationship between olfactory dysfunction and features of the trigeminal system has also been studied in animals. Short-term anosmia has been induced by ZnSO₄ in rats. After that, a significant increase in c-fos expression has been found in cells of the spinal trigeminal nucleus caudalis, which is involved in the transmission of orofacial sensory information (Kalueff and others 2001). These data could indicate a higher sensory transmission in the trigeminal system of anosmic rats (Hunt and others 1987).

An analogous, electrophysiological study has been performed. 3-methylindole was used to induce degeneration of rats’ olfactory mucosa. Nasal mucosal potentials were measured in response to vanillin (the electro-olfactogram [EOG]) and CO₂ (the NMP). In contrast to the findings of the present study, both NMP and EOG responses were depressed. However, EOG showed larger impairment than NMP responses. Thus, the authors speculated that 3-methylindole, in addition to olfactory tissue, would also damage free endings of the trigeminal nerve (Krutsch and others 2000). Thus, in order to test the hypothesis of ongoing adaptation in the trigeminal system, an animal model should be investigated where it is proven that the olfactory degeneration-inducing agent has no direct influence on the trigeminal nerve.

Although there is evidence that the NMP is not an epiphenomenon of a reflex (Thürauf and others 1991, 1993) and that is generated locally, the temporal discrepancy between NMP and ERP peak latencies could lead to another interpretation. It could be that central signals—represented by the ERP—normally exert inhibitory control over peripheral activity, which would be represented by the NMP. In the absence of feedback connections in the patient group, this could then lead to a “disinhibition” of NMP responses resulting in an amplification of the peripheral response.

When measuring central electrophysiological and behavioral responses, a different picture is found. Previous studies, and—in parts—the present one, showed anosmic patients to exhibit a lower sensitivity on central electrophysiological and behavioral measures when compared with controls (Hummel and others 1996, 2003; Kendal-Reed and others 1998; Gudziol and others 2001; Walker and others 2001).

For example, 2 studies investigated the intensity of irritation as a measure of trigeminal sensitivity. Anosmic patients and healthy controls were compared. In both studies, in analogy to the present one, patients were found to rate irritating substances as less intense (Kendal-Reed and others 1998; Walker and others 2001).

However, also contrasting results to the present study can be found in literature. Anosmic and hyposmic patients were found to score lower than controls on a lateralization task (Hummel and others 2003). This could not be confirmed for ICA patients in the present study, although in both age groups average scores were lower in the patients group. Interestingly, though the same technique as in the earlier study was applied, all groups had higher scores in the present study. The reason for this is unclear. However, it might be that differences between patients and control were not significant due to a ceiling effect because the task was too simple to separate between patients and controls.

Another study revealed differing results from the present study. Early tERP components were found to be smaller in patients with olfactory disorders when compared with controls (Hummel and others 1996a). No such difference could be found in the present study in patients with congenital anosmia.

In the following, we will discuss if and under which circumstances the results of the present study can be compared with previous ones and how differences between this and earlier studies can be explained.

First, patients in the present study cannot be directly compared with those investigated in prior studies. ICA patients have a completely different history of anosmia than patients with AA; they never have had a functioning olfactory system. Thus, it remains speculative if data assessed in patients with congenital anosmia and patients with AA can be compared. If not, the results of the present study would be applicable for ICA patients exclusively and not for AA patients.

On the other hand, in contrast to the prior studies, in this investigation a set of patients were investigated who were exclusively anosmic. The anosmia was confirmed by a number of different, sophisticated methods. Thus, ICA patients’ results for trigeminal sensitivity are not blurred by a working olfactory system, which is known to influence trigeminal perception (Cain and Murphy 1980; Livermore and others 1992). In this scenario, a reduced ability to lateralize trigeminal stimulants and smaller early components in tERP would mainly be a feature of patients with an impaired but functioning olfactory system.

Under the following 2 assumptions, another hypothesis could be drawn. 1) The trigeminal system of patients with both congenital and AA is not affected differently. 2) Hyposmia is an intermediate on a continuum between anosmia and normosmia. Then, ICA patients would correspond to patients with the longest imaginable absence of a functioning olfactory system. They would correspond to a virtual endpoint of the trigeminal system’s changes in AA patients. It has been shown that the AA patients’ trigeminal system undergoes changes over time. Two previous studies investigated the relationship between duration of olfactory dysfunction and trigeminal sensitivity. In one study, on the patients’ ability to localize lateralized stimuli, a significant correlation between the lateralization score and the duration of olfactory dysfunction was observed; patients with longer lasting olfactory dysfunction had better results in the lateralization task than those with a shorter history of olfactory loss (Hummel and others 2003). Similarly, a positive correlation between amplitudes P1N1 of tERP and duration of olfactory disorders was observed (Hummel and others 1996a). The amplitude P1N1 belongs to the early ERP components, which are known to be linked to exogenous factors, for example, stimulus concentration, and also to utilization time at the receptor (Pause and Krauel 2000; Frasnelli and others 2003). Thus, it seems that the trigeminal system of AA patients recovers over time. However, previous studies indicate that this recovery takes years to develop (Hummel and others 1996a, 2003). Data from the present study suggest that the responsiveness of the trigeminal system of AA patients could reach...
normal or slightly subnormal levels, confounded only by the age-related decline of trigeminal sensitivity (Frasnelli and Hummel 2003). To test these issues, longitudinal investigations of AA patients are currently underway.

In the present study, ICA patients had similar tERP and scores in the lateralization task as controls, which is in contrast to earlier studies in AA patients (Hummel and others 1996a, 2003). Although this could be caused by general differences between ICA and AA patients, in the following, we will discuss a possible alternative explanation for these findings.

As stated above, in the present study, ICA patients had similar tERP to healthy controls. ERP—and especially early ERP components—are mainly determined by peripheral activation (Paus and others 1997). Peripheral activation is accessible by means of the NMP (Kobal 1985; Thüräuf and others 1991, 1993; Lötsch and others 1997; Frasnelli and Hummel 2003). The NMP was found to be larger in the ICA patients than in the control group. Therefore, the ICA patients could be expected to also show higher early tERP amplitudes. This was not the case and it can be speculated on the rationale. It could be that the trigeminal signal is reinforced on a (early) cerebral level in all subjects with a functioning olfactory system, leading to a relatively higher activation when compared with subjects with a nonfunctioning olfactory system, where it is not reinforced.

As a result, early ERP components would be larger in healthy subjects when compared with AA patients (Hummel and others 1996a). In addition, this could explain the similarities in ERP responses of healthy controls and ICA patients (present study), with the latter having a larger peripheral input.

Thus, it seems that for full functionality, the trigeminal system relies on a working olfactory system. It can be speculated about the underlying mechanisms: in healthy subjects, the sensitivity of the trigeminal system seems to be amplified by a constant activity in the olfactory system. Central interactions between the olfactory and the trigeminal system have been shown on a behavioral level. Olfactory stimulation modulated trigeminal sensations even when the irritant was presented to one nostril and the odorant to the other (Cain and Murphy 1980). It has also been shown that trigeminal stimuli activate brain areas that are also involved in the processing of olfactory sensations, for example, the ventral insula and the middle frontal gyrus (Hummel and others 2005).

For the measurements of tERP and intensity ratings, CO₂ was used, which is commonly seen as pure trigeminal stimulant. However, it cannot be excluded that CO₂ also activates olfactory neurons. Thus, the hypothesis put forward here implies either that CO₂ also activates the olfactory system or that olfactory/trigeminal modulation occurs even if the olfactory system is not excited exogenously.

In summary, from the results of the present study, one could propose a model of mixed sensory adaptation/compensation in the interactions between olfactory and the trigeminal system. In this model, the primary trigeminal activation is reduced on a mucosal level in healthy subjects due to adaptation. On a central level, the trigeminal signal is amplified in subjects with a functioning olfactory system. This processing of trigeminal input determines functions of the trigeminal system, for example, it allows the subjects to localize lateralized stimuli.

Finally, the present study confirmed the known decline in trigeminal sensitivity with age, which starts at a peripheral level (Frasnelli and Hummel 2003). This could also be detected in tERP recordings and the lateralization task.

Conclusion
In the present study, ICA patients were found to have a higher peripheral trigeminal responsiveness. On higher central levels, healthy controls appeared to be equally sensitive or even more sensitive compared with ICA patients. These results could support a model of mixed sensory adaptation/compensation in the interactions between olfactory and the trigeminal system.

Notes
This study was supported by Philip Morris USA Inc. and Philip Morris International. Conflict of Interest: None declared.

Address correspondence to J. Frasnelli, Montreal Neurological Institute, McGill University, 3801 University Street, Room 276, Montreal, Quebec H3A 2B4, Canada. Email: frasnelli@yahoo.com.

References


