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Mexico City Air Pollution Adversely Affects Olfactory Function and Intranasal Trigeminal Sensitivity

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Abstract

Surprisingly little is known about the effects of big-city air pollution on olfactory function and even less about its effects on the intranasal trigeminal system, which elicits sensations like burning, stinging, pungent, or fresh and contributes to the overall chemosensory experience. Using the Sniffin' Sticks olfactory test battery and an established test for intranasal trigeminal perception, we compared the olfactory performance and trigeminal sensitivity of residents of Mexico City, a region with high air pollution, with the performance of a control population from the Mexican state of Tlaxcala, a geographically comparable but less polluted region. We compared the ability of 30 young adults from each location to detect a rose-like odor (2-phenyl ethanol), to discriminate between different odorants, and to identify several other common odorants. The control subjects from Tlaxcala detected 2-phenyl ethanol at significantly lower concentrations than the Mexico City subjects, they could discriminate between odorants significantly better, and they performed significantly better in the test of trigeminal sensitivity. We conclude that Mexico City air pollution impairs olfactory function and intranasal trigeminal sensitivity, even in otherwise healthy young adults.

Key words: air pollution, humans, olfactory function, trigeminal sensitivity

Introduction

Although air pollution is a major health problem in many large cities (e.g., Calderón-Garcidueñas et al. 1996, 2009; Baldasano et al. 2003; Molina and Molina 2004a, 2007; Berglind et al. 2009), little is known about the possible effects of this on olfactory function, and despite extensive evidence of pathological effects on the cellular structure of the nasal epithelium (Calderón-Garcidueñas et al. 1996, 1997, 1998, 2000, 2003, 2009). In a first study (Hudson et al. 2006), we recently compared the olfactory performance of residents of Mexico City, a region with notoriously high levels of air pollution (Blake and Rowlands 1995; Valverde et al. 1997; Calderón-Garcidueñas et al. 1998, 2000, 2003; Molina and Molina 2002, 2004b; Secretaría de Medio Ambiente del Gobierno del Distrito Federal 2006; Secretaría de Medio Ambiente y Recursos Naturales—Instituto Nacional de Ecología 2006a, 2006b; Molina et al. 2007), with the performance of residents of the neighboring Mexican state of Tlaxcala, a geographically similar region with markedly lower levels of air pollution (cf., Calderón-Garcidueñas et al. 2006; Secretaría de Medio Ambiente y Recursos Naturales—Instituto Nacional de Ecología 2006b). In this previous study, we tested the ability of subjects to detect, discriminate, describe, and name common olfactory stimuli from everyday life. These were 2 international beverages (instant coffee and a commercial orange drink preparation) and 2 Mexican beverages (horchata and atole) presented in polyethylene squeeze bottles. We chose these substances to maximize the ecological validity of the stimuli and the ability of subjects to describe and to accurately name them (cf., Ayabe-Kanamura et al. 1998; Distel et al. 1999; Distel and Hudson 2001). Tlaxcala residents performed significantly better than Mexico City residents on tests of odor detection and discrimination, but the 2 groups performed equally well on description and naming. Deficits in olfactory performance were apparent even for young, otherwise healthy adults.

Although the results of the previous study provided support for our prediction that Mexico City air pollution impairs olfactory function, the test methods used had certain

limitations. The stimuli were not standardized in such a way as to allow comparison with other studies, it was time consuming to prepare them fresh each day, and most importantly, the method of stimulus preparation and delivery may not have been precise enough to detect differences on the more cognitive tasks. In the present study, we therefore decided to reinvestigate the effect of big-city air pollution on olfactory function using a well-established and standardized method, the Sniffin' Sticks test battery (Hummel et al. 1997; Kobal et al. 2000). Additionally, we decided to make a more complete investigation of the effect of air pollution on chemosensory function by asking whether impairment is also present in the nasal trigeminal system.

What is commonly known as the sense of smell is, in fact, composed of multiple sensations predominantly mediated by 2 distinct neural pathways, the olfactory and the somatosensory (trigeminal) systems (e.g., Elsberg et al. 1935; Hudson et al. 1994; Laska et al. 1997; Hummel et al. 2009). Few chemosensory stimulants produce exclusively olfactory or trigeminal sensations (i.e., stinging, burning, or pungent), and the great majority possess characteristics of both odor and irritation (von Skramlik 1925; Doty et al. 1978; Cometto-Muñiz and Cain 1991, 1998; Hummel 2000). The 2 systems are closely connected functionally already at the level of the olfactory epithelium or the olfactory bulb (Bouvet et al. 1987; Schaefer et al. 2002) and continuing to the level of the piriform cortex (Boyle, Frasnelli, et al. 2007; Boyle, Heinke, et al. 2007; Hummel et al. 2009). It is notable, however, that although both systems contribute to the overall chemosensory experience, they may have evolved for different purposes. An important function of the intranasal trigeminal system is to act as a sentinel of the airways, reflexively stopping inspiration to prevent inhalation of potentially life-threatening substances (Gudziol and Gramowski 1987; Walker et al. 2001; Scheibe et al. 2006), whereas a major function of the olfactory system is to enable the learning of odors relevant to an individual's particular life experiences and environment (Hudson 1999).

Given the contribution of both the olfactory and trigeminal systems to odor perception via the intranasal sensory surface, and notable pathological effects of air pollution on the cellular structure of the epithelium (Calderón-Garcidueñas et al. 1996, 1997, 1998, 2000, 2003, 2009), we expected that residents of Mexico City would show significantly poorer performance than residents of Tlaxcala on trigeminal as well as on olfactory tasks.

Materials and methods

Subjects

Sixty healthy, nonsmoking, unpaid volunteers 18–35 years of age were recruited from either the Universidad Nacional Autónoma de México (UNAM), Mexico City (30 subjects exposed to high levels of air pollution characteristic of the south of Mexico City where the main campus of UNAM is located; mean age = 25.53 years, standard deviation, SD = 4.36), or from the Universidad Autónoma de Tlaxcala (UAT) (30 subjects of similar socioeconomic background to the Mexico City subjects; mean age = 24.50 years, SD = 3.82, and living in a region with a similar climate, altitude, and other geographic characteristics to nearby Mexico City but separated from it by a mountain range and with markedly lower levels of air pollution (Calderón-Garcidueñas et al. 2006; Secretaría de Medio Ambiente y Recursos Naturales—Instituto Nacional de Ecología 2006b). Mexico City subjects had lived for at least the past 10 years and most, all their life in Mexico City, and Tlaxcala subjects had lived all their life in Tlaxcala or in neighboring regions other than Mexico City. None of the subjects worked in an environment exposing them to toxic chemicals. There were 15 women and 15 men in each group and none with a history of major olfactory disturbance. Procedures conformed to the Declaration of Helsinki for Medical Research involving Human Subjects and to the guidelines for the treatment of human subjects in research of the Instituto de Investigaciones Biomédicas, UNAM, Mexico.

Test procedures

The Mexico City subjects were tested in a well-ventilated room at the Instituto de Investigaciones Biomédicas, UNAM, and the Tlaxcala subjects in a well-ventilated room at the Centro Tlaxcala de Biología de la Conducta, UAT. We obtained demographic information (age, sex, smoking history, period of residence in Mexico City or Tlaxcala, work environment, and medical history) and informed consent before the start of testing.

The study had 2 parts: an assessment of olfactory performance using a standardized Sniffin' Sticks test (see below), followed by an assessment of nasal trigeminal sensitivity using a technique described previously (Kobal et al. 1989; Berg et al. 1998; Hummel et al. 2003; Dalton et al. 2006). Each subject was tested in a single session lasting a maximum of 58 min. Tests were conducted from November 2008 to February 2009 (the winter dry season in highland central Mexico) so as to exclude a possible effect of season between the 2 populations. Tlaxcala has been used as a control region in previous clinical studies of both human and canine subjects (Calderón-Garcidueñas et al. 2003, 2006; see also Hudson et al. 2006), in part because of similar air pressure, temperature, and humidity, which could affect olfactory function (Kuehn et al. 2008) and because of substantially lower levels of air pollution (Secretaria de Medio Ambiente y Recursos Naturales—Instituto Nacional de Ecología 2006b).

Olfactory performance

Odorants were presented to blindfolded subjects (except for the identification test, see below) following an established

procedure (Hummel et al. 1997; Kobal et al. 2000). Briefly, odorants were presented in felt-tipped marker pens, 14 cm long, with an inner diameter of 1.3 cm, and instead of dye, filled with 4 mL of liquid odorant or odorant dissolved in propylene glycol. At the moment of testing, the cap was removed by the experimenter who held the tip of the pen approximately 2 cm in front of the subject's nostrils for approximately 2–3 s. Subjects were instructed when to sniff and could sample each stimulus only once.

The standard Sniffin' Sticks procedure tests subjects' ability to detect an odorant (threshold), to distinguish between odorants, and to name them using a verbal checklist. One advantage of combining these different measures of olfactory function is to help identify where in the chemosensory pathway functional impairment occurs. Another is that using only one measure of olfactory function carries the risk of failing to detect olfactory loss (Dalton et al. 2006; Lötsch et al. 2008). We were particularly interested if when applying this standardized and internationally used procedure we could replicate the findings of our previous study showing a significant reduction in the ability of Mexico City residents to detect and to distinguish between odorants, but little or no reduction in the ability to describe and to correctly name them. Such a disjunction in performance would imply that the negative effects of air pollution on olfactory function are due principally to damage at the periphery of the system, leaving centrally mediated cognitive processes largely intact (discussion in Hudson et al. 2006).

Threshold

Subjects' ability to detect 2-phenyl ethanol was determined using a single-staircase, 3-alternative forced-choice procedure. Sixteen dilutions were prepared in a geometric series starting with a 4% solution (dilution ratio 1:2 in propylene glycol). In each trial, 3 pens were presented individually in randomized order, 2 containing only the solvent and the third the odorant, and subjects were instructed to identify the pen that smelled different (i.e., that contained 2-phenyl ethanol). The interval between presentation of pens within a triplet was approximately 3 s and between triplets approximately 20 s. The staircase was reversed when the odor was correctly identified on 2 successive trials. Threshold was defined as the mean of the last 4 of 7 staircase reversals. Subjects' scores could thus range between 0 (minimum sensitivity/anosmic for 2-phenyl ethanol) and 16 (maximum sensitivity).

Discrimination

Again using a 3-alternative forced-choice paradigm, 16 triplets of pens containing concentrations of odorants well above threshold for normosmics were presented in randomized order, with 2 containing the same and 1 a different odorant. Subjects had to determine which one of the 3 pens smelled different. As for threshold determinations, the interval between presentation of pens within a triplet was approximately 3 s and between triplets approximately 20 s. Because 16 triplets were tested, subjects' scores could range from 0 to 16.

Identification

Subjects were presented with 16 common odorants in the same order for all subjects and asked to choose the most appropriate (Spanish language) descriptor from a list of 4 plausible possibilities (e.g., citral [lemon] as target vs. apple, peach, and grapefruit as distractors). Odorants were well above threshold for normosmics, the interval between presentation of pens was approximately 10 s, and again subjects' scores could range from 0 to 16.

Overall performance

For each subject, results of the 3 subtests were summed to give a composite Threshold–Discrimination–Identification (TDI) score (maximum of 16 + 16 + 16 = 48; Wolfensberger et al. 2000; Hummel et al. 2007). Scores of 31 and above are considered to represent normal olfactory ability, scores between 30.75 and 16 are considered to represent impaired olfactory ability (hyposmia), and scores below 16 to represent functional anosmia (Kobal et al. 2000).

Trigeminal sensitivity

After the olfactory tasks, subjects were tested for nasal trigeminal sensitivity using a method described previously (Roscher et al. 1996; Wysocki et al. 1997; Berg et al. 1998; Hummel et al. 2003; Dalton et al. 2006). For this, they were presented with 2 250-mL polyethylene squeeze bottles with Teflon nosepieces that fit into the nostrils. The nosepieces were covered with disposable plastic caps that were replaced for each subject. Whereas the target bottle contained 30 mL of ≥98% eucalyptol (Fluka, Germany), a stimulus that elicits both olfactory and nasal trigeminal responses in humans and that has been previously used in lateralization tests (Doty et al. 1978; Berg et al. 1998; Hummel et al. 2003), the odorless control bottle contained only ambient air. The headspace of the bottles was used to stimulate both sides of the nose independently but simultaneously during the same inspiration, and the subject's task was to identify the side of the nose receiving the stimulus. The side of stimulation was pseudorandomized across trials in the same manner for all subjects. Stimuli were presented using a hand-held squeeze device that simultaneously delivered a constant volume (15 mL) of air to each nostril (Figure 1). Subjects received 40 trials (20 deliveries of eucalyptol to each nostril) from which we calculated the percent of correct responses. This method is based on the well-established finding that although subjects have difficulty identifying the nostril receiving a purely olfactory stimulus, they can readily do this for stimuli with a trigeminal component (Cometto-Muñiz and Cain 1998; Hummel et al. 2003; Wysocki et al. 2003; Dalton et al. 2006).

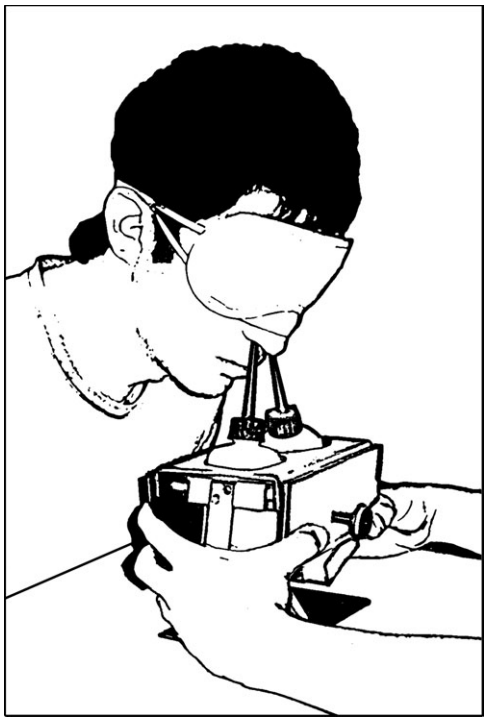

Figure 1 Hand-held squeeze device used for testing the ability of subjects to identify the nostril receiving a trigeminal stimulus (eucalyptol). A mechanically limited maximum squeeze of 2 polyethylene bottles simultaneously delivered equal volumes of headspace (1 containing the odorant) to the 2 nostrils.

Data treatment and analysis

Because performance scores were not always normally distributed (Kolmogorov–Smirnov tests) and most were based on frequencies, performance data for the 2 groups are graphed as medians and interquartile ranges and compared using nonparametric Mann–Whitney *U* tests. Two-tailed tests were performed throughout using the statistical program SYSTAT 12 and taking $P \leq 0.05$ as the level of significance.

Results

There was no significant difference between the 2 groups in the time of day at which tests were undertaken ($t_{58} = 0.39$, $P = 0.70$), nor in session duration ($t_{58} = 1.05$, $P = 0.30$). Because we did not find difference between the sexes on any measure, scores for men and women were combined for the final analysis.

Olfactory performance

Threshold

Subjects from Tlaxcala detected 2-phenyl ethanol in the single-staircase, 3-alternative forced-choice procedure at significantly lower concentrations than Mexico City subjects (Figure 2a; Mexico City: mean = 9.57, SD = 2.86; Tlaxcala: mean = 11.42, SD = 1.65. Mann–Whitney *U* test: $U = 653_{30,30}$, $P < 0.003$). Based on the median scores, this represented a 2- to 4-fold difference in the concentration needed to detect the presence of this stimulus.

Discrimination

In general, the subjects from Tlaxcala were better able to distinguish the target stimulus in the 3-alternative forced-choice tests than the Mexico City subjects (Figure 2b). This difference was also significant (Mexico City: mean = 11.83, SD = 2.05; Tlaxcala: mean = 13.03; SD = 1.43. $U = 601_{30,30}$, $P < 0.02$).

Identification

Although the odorants in this test had been originally chosen for their familiarity for Europeans, with the exception of turpentine and apple, our subjects had little difficulty identifying them. We did not find a significant difference between the 2 groups on this task (Figure 2c; Mexico City: mean = 12.73; SD = 1.68; Tlaxcala: mean = 12.63; SD = 1.45. $U = 428_{30,30}$, $P = 0.75$).

Overall performance

The Tlaxcala subjects had significantly higher TDI scores than the Mexico City subjects, expressed as the sum of scores obtained in the threshold, discrimination, and identification tests reported above (Figure 2d; Mexico City: mean = 34.13, SD = 4.21; Tlaxcala: mean = 37.01, SD = 2.53; $U = 638_{30,30}$, $P = 0.006$). In fact, 6 Mexico City subjects (20%) had scores below the lowest-scoring Tlaxcala subject, and 4 Tlaxcala subjects (13%) had scores above the highest-scoring Mexico City subject. Although 6 Mexico City subjects had scores identifying them as hyposmic, no Tlaxcala subject had a score in this category.

Trigeminal sensitivity

In the test requiring subjects to identify the side of the nose receiving trigeminal stimulation, the Tlaxcala subjects again performed significantly better than the Mexico City subjects (Figure 3; Mexico City: mean = 28.20, SD = 7.42; Tlaxcala: mean = 32.33, SD = 6.065. $U = 603.5_{30,30}$, $P = 0.023$).

Discussion

The present findings basically confirm the findings of our previous study reporting a significant reduction in olfactory sensitivity but not in the ability to identify common odorants in subjects from Mexico City, a region of high urban air pollution, compared with subjects from the rural state of Tlaxcala, a geographically similar region but with low air pollution (Hudson et al. 2006). The findings are also consistent with the extensive literature reporting harmful effects on chemosensory function of chronic exposure to potentially harmful substances in different work environments (e.g., Cometto-Muñiz and Cain 1991; Berglund et al. 1992; Smeets and Dalton 2002; Smeets et al. 2002; Hastings and Miller 2003; Cheng et al.

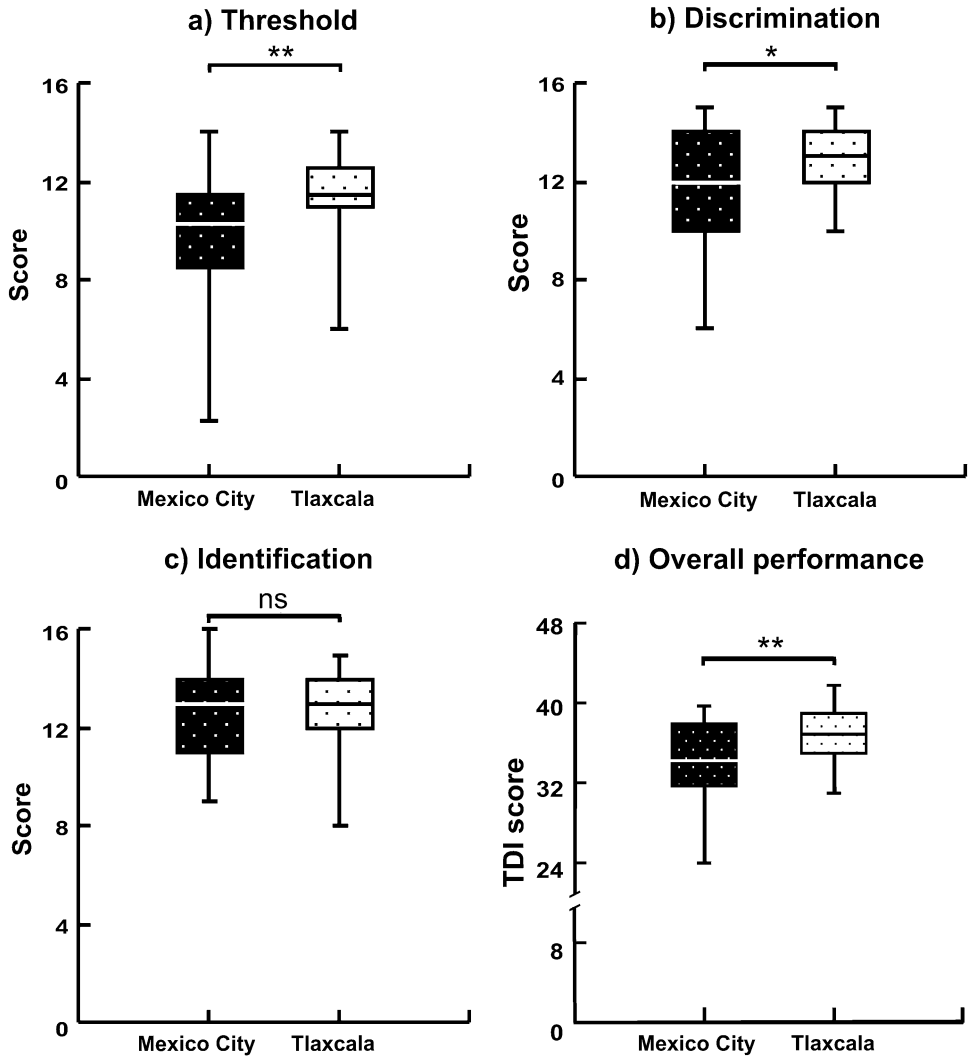

Figure 2 Performance of subjects from Mexico City and Tlaxcala on the 3 tests of olfactory performance (a–c) as well as their TDI scores representing the sum of their scores on these tests (d). For each of the 3 tests, subjects could obtain a maximum score of 16 correct responses and consequently a maximum TDI score of 48. Box plots: horizontal lines within boxes give medians, boxes' horizontal limits give the interquartile ranges, and whiskers give the absolute ranges. *$P < 0.05$, **$P < 0.01$, ns = not significant (Mann–Whitney U tests).

2004; Vent et al. 2004; Zibrowski and Robertson 2006; Heiser et al. 2009; Kacha et al. 2009). The similarity between the results of this and our previous study, and despite differences in test methods and odor stimuli, suggests the reliability of the findings. Furthermore, the present study extends previous findings by demonstrating an adverse effect of big-city air pollution on nasal trigeminal function. This is potentially important given the contribution of the trigeminal system to odor perception (e.g., Hudson et al. 1994; Laska et al. 1997; Hummel and Livermore 2002; Boyle, Heinke, et al. 2007; Frasnelli and Hummel 2007; Frasnelli et al. 2009) and to warning of the presence of toxic or noxious substances (Silver 1992; Dalton et al. 2006; Scheibe et al. 2006).

These findings are all the more notable as they are likely to be conservative. Our subjects were healthy young adults, all nonsmokers and all from socioeconomic backgrounds ensuring good nutrition and good general hygiene and health care. The impaired nasal chemosensory function of the Mexico City subjects is therefore unlikely to have been due to health problems other than the effect of air pollution. Among the substantial poorer sectors of Mexico City's heterogeneous population or in older subjects (Hudson et al. 2006), the extent of chemosensory loss may be even greater.

Apart from recent findings possibly indicating pathology at the level of the olfactory bulb as a result of environmental pollution (Calderón-Garcidueñas et al. 2009), there is presently no direct information on the precise nature of the damage impairing olfactory and trigeminal function or on the level(s) in these systems where this occurs. Nevertheless, evidence for a broad spectrum of pathological effects of air pollution on tissue within the nasal cavity of humans

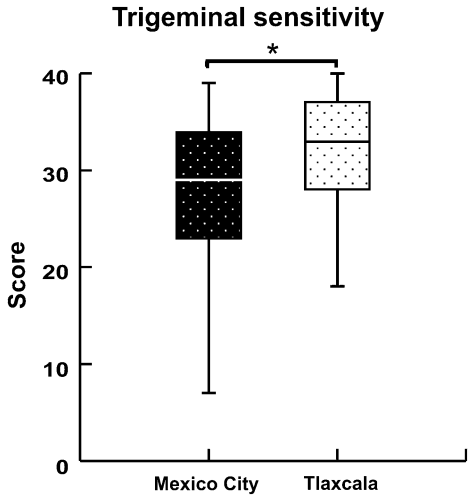

Figure 3 Ability of subjects from Mexico City and Tlaxcala to correctly identify the nostril receiving the trigeminal stimulus eucalyptol when presented as shown in Figure 1. Subjects could obtain a maximum score of 40 correct responses. Box plots: horizontal lines within boxes give medians, boxes' horizontal limits give the interquartile ranges, and whiskers give the absolute ranges. *$P < 0.05$ (Mann–Whitney U test).

(e.g., Calderón-Garcidueñas et al. 1996, 1997, 1998, 2001; Valverde et al. 1997; Hardisty et al. 1999) and dogs (Calderón-Guarcidueñas et al. 2003) suggests that the perceptual deficits we report here and in our previous study (Hudson et al. 2006) were due primarily to damage at the peripheral level. Consistent with this was the equally good performance of the Mexico City and Tlaxcala subjects on the odor identification task, which because it involved the presentation of odorants well above threshold, presumably depended more on centrally mediated associative memory functions than did the odor threshold or discrimination tasks (see Hudson et al. 2006 for similar findings; Lötsch et al. 2008). The good performance of the 2 groups on this task also suggests both groups to have been equally motivated and equally able to handle the test situation.

Clear evidence of deficits in olfactory and nasal trigeminal function in otherwise healthy young adults exposed to high levels of urban air pollution raises important public health questions regarding the age at which such pathologies first become apparent and if and to what age they are reversible.

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