ORIGINAL ARTICLE

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Differences in nasal irritant sensitivity by age, gender, and allergic rhinitis status

Abstract *Objectives*: Sensory (eye, nose, and throat) irritation is an important component of non-specific building-related illness ("sick-building syndrome"). Inter-individual variability in susceptibility to upper airway/mucous membrane irritants is suspected epidemiologically, but has been neglected experimentally. We wished to document population variability in nasal irritant sensitivity, as indexed by threshold measurements of sensory acuity. We hypothesized that younger subjects, women, and allergic rhinitis sufferers would display lower sensory thresholds than would older subjects, men, and rhinitis non-sufferers. *Methods*: We evaluated Sixty human subjects (stratified by age, gender, and seasonal allergy status), using two different test systems: (1) carbon dioxide (detection) and (2) *n*-propanol (localization). We obtained carbon dioxide (CO_2) detection thresholds using an ascending concentration series, presenting 3-s pulses of CO_2, paired with air in random order, by nasal cannula. Localization thresholds were obtained by the simultaneous presentation of *n*-propanol vapor (ascending concentrations in air) and blanks (saturated water vapor in air) to opposite nostrils, with laterality randomized. Threshold data were log-transformed to satisfy normality and analyzed by population marker via ANOVA and linear regression. *Results*: Test–retest variability was greater for volatile organic compound (VOC) localization than for CO_2 detection (r = 0.50 and 0.75, respectively); the two measurements were, however, positively correlated (r = 0.48; $P < 0.001$).

Age predicted both (log-transformed) VOC localization thresholds ($P < 0.0001$) and (log-transformed) CO_2 thresholds ($P < 0.01$), with younger age predicting lower thresholds. Female gender predicted lower CO_2 detection ($P < 0.05$) but not VOC localization thresholds ($P = 0.10$). Nasal allergies predicted lower VOC localization ($P < 0.05$) but not CO_2 detection thresholds ($P = 0.52$). *Conclusions*: Consistent with epidemiological reporting patterns in so-called problem buildings, nasal irritant sensitivity appears to be non-randomly distributed in the population, with significant variability predicted by age, gender, and the presence of allergic rhinitis.

Keywords Sensory irritation · Demographics · Allergic rhinitis · Sick-building syndrome · VOCs

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Introduction

Sensory (eye, nose and throat) irritation warns of exposure to air pollutants and figures prominently in the symptom complex referred to as sick-building syndrome (Cometto-Muñiz and Cain 1992). Epidemiological studies conducted in so-called problem buildings suggest the importance of personal risk factors in the genesis of upper respiratory tract symptoms. More specifically, women, individuals with pre-existing allergic rhinitis, and younger individuals, are more likely to report indoor air symptoms, including eye, nose and throat irritation, than are men, rhinitis non-sufferers, and older individuals (Brasche et al. 2001; Cummings et al. 1991; Hall et al. 1993; Menzies and Bourbeau 1993; Muzi et al. 1998; Stenberg and Wall 1995) (see Table 1). This symptom complex is an important source of both personal discomfort and lost productivity [one estimate of its total cost impact in the USA being $40–200 billion annually (Fisk 2000)].

Indoor air quality problems are thought to be due to both physical (i.e., temperature and humidity) and chemical factors. Chemical irritants potentially found in indoor air include combustion products (from cigarette

Table 1 Epidemiological risk factors for symptom reporting in "problem buildings"

Author	Gender (female)	Nasal allergies	Age (younger)
Brasche et al. (2001)	x	x	x
Cummings et al. (1991)		x	
Hall et al. (1993)	x	x	
Menzies and Bourbeau (1993)	x	x	x
Muzi et al. (1998)	x		
Stenberg and Wall (1995)	x		

smoke, vehicle exhaust, and malfunctioning combustion appliances), reactive chemicals derived from cleaning products (e.g., chloramines, ammonia, acetic acid), and a wide variety of volatile organic compounds (VOCs) off-gassed from construction materials, interior furnishings, consumer products and microbial sources (Hodgson 2002; Jaakkola et al. 1994; Junker et al. 2001; Molhave 1992; Ten Brinke et al. 1998). Extensive studies have been carried out that compare the sensory irritant potency of various VOCs; however, documentation of inter-individual variability is not a prominent component of these studies (Cometto-Muñiz and Cain 1993, 1998; Shusterman 2002). Nevertheless, when demographic predictors of symptom reporting have been recognized in epidemiological field studies, they have generally been assumed to be of sociological, rather than biological, significance (Brasche et al. 2001; Ryan and Morrow 1992; Stenberg and Wall 1995).

We previously demonstrated the feasibility of studying population variability in nasal irritant sensitivity (sensory acuity) in a pilot investigation that examined a small group of subjects stratified by gender and nasal allergy status (Shusterman et al. 2001). Two test systems were employed in this study, one utilizing the odorless irritant carbon dioxide (CO_2), which produces transient nasal irritation via its hydration to carbonic acid (Stevens and Cain 1986; Shusterman and Balmes 1997a, 1997b), and the other utilizing the odorous VOC *n*-propanol, for which threshold measurements can be generated by the localization task (Cometto-Muñiz and Cain 1998; Hummel 2000; Kobal 1989; Schneider and Schmidt 1967; Von Skramlik 1925; Wysocki et al. 1992). Replicate measurements of CO_2 detection and VOC localization indicated that gender, more than allergy status, predicted lower thresholds (i.e., greater sensitivity). Here, we report on a full-scale study of 60 subjects stratified on age, gender, and allergy status. A priori, we hypothesized that younger subjects, women, and allergic rhinitis sufferers would display lower sensory thresholds than would older subjects, men, and rhinitis non-sufferers.

Methods

Subject recruitment

Subjects aged between 18–69 years were recruited through posters and on-line advertisements. Potential subjects with chronic cardiopulmonary diseases (including asthma), active smoking (within 6 months), who were pregnant or lactating, or receiving medications having anticholinergic or antihistaminic side effects, were excluded. Signed informed consent was obtained. Subjects whose questionnaire responses indicated either seasonal allergic rhinitis (SAR) or no rhinitis (NR) were referred for allergy skin testing, including 16 common aeroallergens/mixes, plus histamine (1.8 mg/ml; AllerMed Laboratories, San Diego, Calif., USA) and saline controls. Skin test results were compared with questionnaire responses for consistency, and subjects were classified as SAR or NR when concordant information was present (discrepant cases being excluded from further testing). A total of 60 subjects was recruited, with the goal of a balanced sample by gender, allergy status, and age stratum (18–34, 35–51, and 52–69 years).

The study was reviewed by the Committee on Human Research of the University of California, San Francisco and fulfills the ethical requirements stated in the Helsinki declaration, including informed consent from all subjects prior to their inclusion in the study.

Psychophysical testing (CO_2 detection and *n*-propanol localization)

All testing took place in a 950 cu. ft climate-controlled chamber located at the University of California, Berkeley, Environmental Engineering and Health Sciences Laboratory. The air supply to the chamber was subjected to both high efficiency particulate (HEPA) and charcoal filtering, with a supply temperature regulated to $22 \pm 1°C$, and relative humidity to $40 \pm 3\%$. Subjects acclimated to the above atmosphere for at least 10 min before being tested. Replicate testing sessions were conducted for each of the two testing systems (CO_2 detection and VOC localization). Testing sessions were separated by at least 1 day, and the testing order (CO_2–VOC–CO_2–VOC or VOC–CO_2–VOC–CO_2) was counterbalanced for each subgroup of subjects within each age stratum (e.g., rhinitic men < 35 years). Allergic rhinitic subjects were tested outside of their allergy season, and any subject reporting "cold" symptoms was re-scheduled after a 2- to 3-week symptom-free period. Subjects were instructed not to eat, drink (other than water), or exercise for 1 h prior to being tested; they were also asked not to wear perfumes, colognes, or aftershaves, on the day of testing.

CO_2 detection thresholds

The CO_2 dilution apparatus has been described in detail elsewhere (Shusterman and Balmes 1997b). Briefly, medical-grade compressed air and CO_2 were delivered to rotameters (flow meters) via electronically controlled solenoid valves to deliver 0% and 15–45% CO_2 vol/vol (5% steps) at a total rate of 5 l/min. The output of these rotameters was delivered to both nostrils via a disposable, non-occlusive nasal cannula, the right nostril being equipped with a standard respiratory flow thermocouple to permit the observation/recording of the respiratory pattern and synchronization of applied stimuli, as noted below.
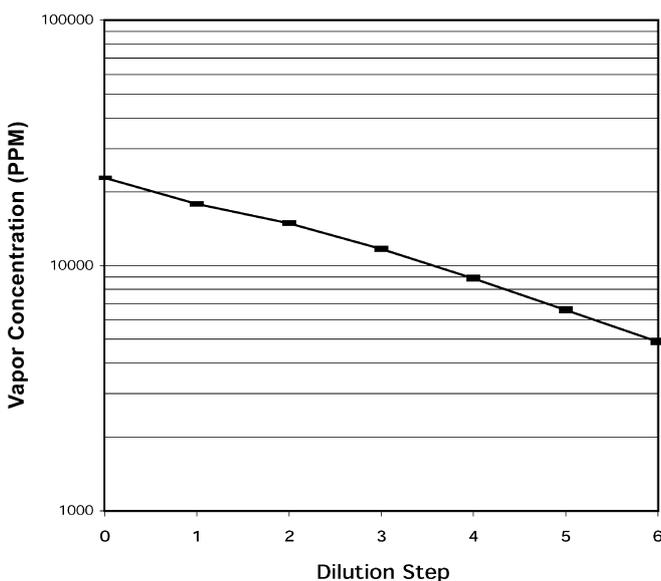
Trials consisted of pairs of 3.0-s stimuli—one air and the other CO_2 diluted in air—synchronized with inspiration. The two stimuli were presented in random order and separated by an inter-stimulus interval of 12–15 s and an inter-trial interval of 60 s. Stimuli were presented in an ascending series, beginning at 0% CO_2, ("sham" discrimination) with five trials being conducted at each level. Subjects were blind with regard to stimulus order and progression, and care was exercised not to provide auditory (or other) cues as to stimulus level. The CO_2 detection threshold was defined as the lowest concentration at which the subject correctly identified all five CO_2 stimuli as being "more irritating" than filtered air blanks. If a subject did not successfully identify all five CO_2 stimuli at the highest presented level (45%), the threshold was listed as 50%.

VOC localization thresholds

Procedures for VOC localization have also been detailed elsewhere (Shusterman et al. 2001). *n*-Propanol dilutions in deionized water, as well as blanks containing an equal volume of deionized water alone, were contained in paired 240-ml polyethylene squeeze bottles. Stimuli and blanks (headspace from the squeeze bottles) were conveyed from bottles to nares via 15-cm lengths of 1.5-mm i.d. flexible plastic tubing, capped with perforated foam earplugs, which anchored tubes in the subjects' nostrils during trials. Stimuli were delivered over an approximately 0.5-s duration.

n-Propanol concentrations were adjusted to achieve a geometric progression of headspace vapor concentrations (target concentration ratio = 1.30 from step-to-step). Stimulus concentrations were determined on a weekly basis during the study, via a model 6850 gas chromatograph equipped with a gas-sampling valve, flame-ionization detector, and non-polar column (Agilent Technologies, Wilmington, Del., USA). We calculated headspace concentrations as areas under the curve (AUCs), utilizing the AUC for undiluted *n*-propanol as the standard; predicted vapor pressure for the standard was derived with the Antoine equation (Kubiek and Eubank 1972). Mean headspace concentrations for the seven steps in the dilution series spanned the range of 4,800–22,700 ppm (Fig. 1), with a coefficient of variation averaging 6.5% (and SEM averaging 92 ppm) for the six dilution steps over 58 determinations spanning the study period. Step-to-step concentration ratios averaged 1.29 ± 0.02 (mean $\pm$ SEM).

The VOC testing protocol consisted of a forced-choice localization procedure with an ascending vapor concentration series, as described above. Subjects signaled their breathing pattern to the tester through hand movements, and at the end of expiration were instructed to sniff gently, at which time the stimulus and blank bottles were simultaneously compressed, delivering approximately 30 ml of headspace from each. After a brief interval, subjects were asked to indicate which nostril experienced the most irritation (defined as burning, stinging, tingling, or simply a cooling sensation). Subjects were asked to focus specifically on irritation, rather than odor. There were six trials per stimulus level, with an inter-trial interval of 60 s. The laterality of stimuli was subjected to limited randomization (equal number of stimuli and blanks were presented to each nostril). Subjects were blind with regard to stimulus order and progression. The lowest stimulus concentration at which a subject correctly identified the laterality of all six stimuli was considered to be the VOC localization threshold.

Data analysis

Data were analyzed on a Macintosh G4 computer using JMP (SAS Institute, Carey, N.C., USA). Data were examined for normality and log-transformed [ln] to achieve normality prior to further analysis. Univariate analyses of normalized data were carried out by ANOVA (discrete explanatory variables) or least-squares regression (continuous explanatory variables). Means $\pm$ SEM were used throughout to convey information on both variance and sub-sample size. Although we recruited a balanced sample of subjects in order to maximize statistical power in univariate analyses, we used multivariate linear regression for the sole purpose of estimating the total variance accounted for by the three explanatory variables together.

Results

Subject panel

The characteristics of the 60 subjects appear in Table 2. The sample was balanced with respect to gender, and quite nearly so by seasonal allergies. Subjects ranged from 19 to 68 years of age; there were more subjects in the middle (35–51 years old) age stratum ($n = 24$) than in the younger or older strata ($n = 18$ each). The seasonal allergic rhinitis group did not differ significantly in age from the non-rhinitis group (40.7 ± 13.2 vs 43.1 ± 15.1 years (mean $\pm$ SD); $P = 0.52$), nor did male subjects differ significantly in their age distribution from female (41.6 ± 14.5 vs 42.1 ± 14.0 years; $P = 0.89$).

Test–retest reproducibility; inter-test comparison

Test–retest variability was greater for VOC localization than for CO_2 detection (r = 0.50 and 0.75, respectively); the two measurements were, however, highly significantly correlated (r = 0.48; $P < 0.001$; Fig. 2).

Fig. 1 Mean ($\pm$ SEM) headspace *n*-propanol concentrations (in parts per million, vol/vol) by dilution step. Gas chromatographic determinations were obtained on a weekly basis during the study. The mean coefficient of variation for all steps combined was 6.5%

Table 2 Characteristics of study subjects

| Age stratum	Rhinitis	Gender	Number	Age (mean $\pm$ SD)
18–34 years	No	Male	4	23.3 ± 4.2
		Female	4	23.0 ± 4.2
	Yes	Male	5	24.0 ± 3.9
		Female	5	28.6 ± 2.5
35–51 years	No	Male	5	43.7 ± 8.6
		Female	6	43.8 ± 7.0
	Yes	Male	7	42.5 ± 5.1
		Female	6	39.4 ± 4.1
52–69 years	No	Male	5	56.6 ± 4.3
		Female	5	60.0 ± 5.6
	Yes	Male	4	59.5 ± 4.8
		Female	4	58.3 ± 5.3
Combined	–	–	**60**	**41.9 ± 14.1**
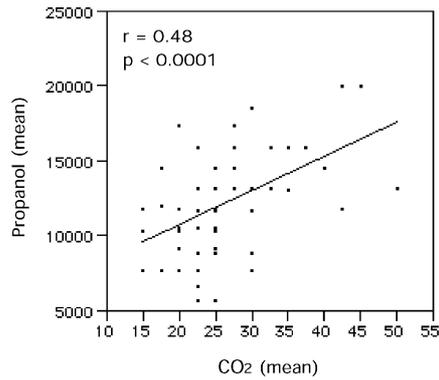
Fig. 2 Inter-test comparison: individual mean CO_2 detection vs VOC localization thresholds ($r = 0.48$; $P < 0.0001$). Number of observations exceeds number of data points due to identical observations
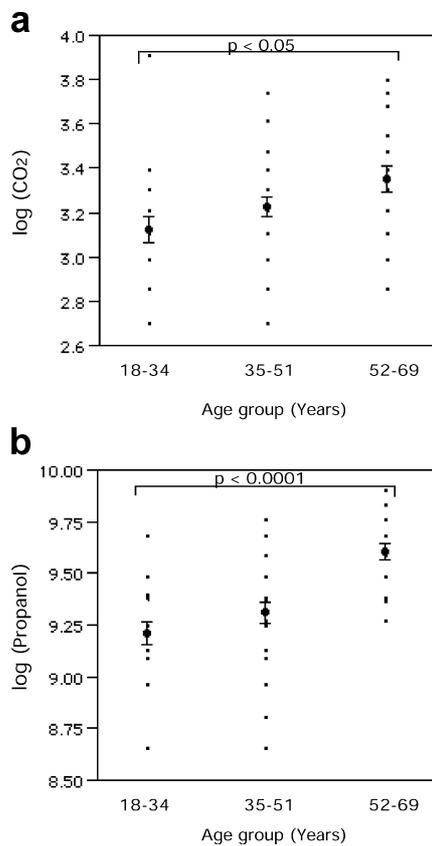
Fig. 3 a Mean ($\pm$ SEM) log CO_2 detection threshold by age range ($f = 3.59$; $P < 0.05$). Number of observations exceeds number of data points due to identical observations. Analysis by age as a continuous variable strengthens results ($f = 8.47$; $P < 0.01$). **b** Mean ($\pm$ SEM) log VOC localization threshold by age range ($f = 11.9$; $P < 0.0001$). Number of observations exceeds number of data points due to identical observations. Analysis by age as a continuous variable yields identical conclusions ($f = 19.2$; $P < 0.0001$)

Threshold variation by subject characteristics

Age range predicted both (log-transformed) VOC localization thresholds ($P < 0.0001$) and (log-trans-
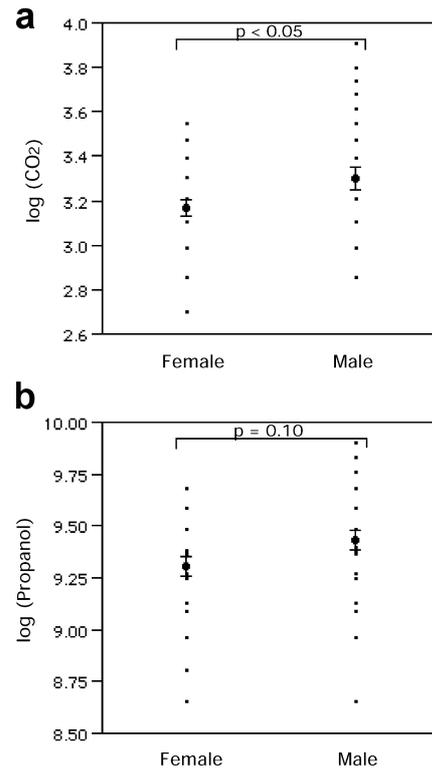
Fig. 4 a Mean ($\pm$ SEM) log CO_2 detection threshold by gender ($f = 4.19$; $P < 0.05$). Number of observations exceeds number of data points due to identical observations. **b** Mean ($\pm$ SEM) log VOC localization threshold by gender ($f = 2.72$; $P = 0.10$). Number of observations exceeds number of data points due to identical observations

formed) CO_2 thresholds ($P < 0.05$), with younger age predicting lower thresholds (Fig. 3). Substitution of age as a continuous variable resulted in a strengthening of the CO_2 (but not VOC) relationship ($P < 0.0001$ each). Female gender predicted lower CO_2 detection ($P < 0.05$) but not VOC localization thresholds ($P = 0.10$; Fig. 4). Nasal allergies predicted lower VOC localization ($P < 0.05$) but not CO_2 detection thresholds ($P = 0.52$; Fig. 5). Multivariate regression indicated that the three explanatory variables together accounted for up to 28% of observed variance in (log-transformed) CO_2 detection and 31% of observed variance in (log-transformed) VOC localization thresholds. Finally, we re-examined the gender effect on observed log (CO_2 threshold) by stratifying subjects by age: < 52 years ($n = 42$) vs ≥ 52 years ($n = 18$). Interestingly, older women differed more from men than did younger women ($P = 0.03$ and 0.28, respectively).

Discussion

With regard to our a priori hypotheses, significant age-related decrements were apparent in both CO_2 detection and VOC localization. Gender, on the other hand, predicted differences in CO_2 detection only (female subjects
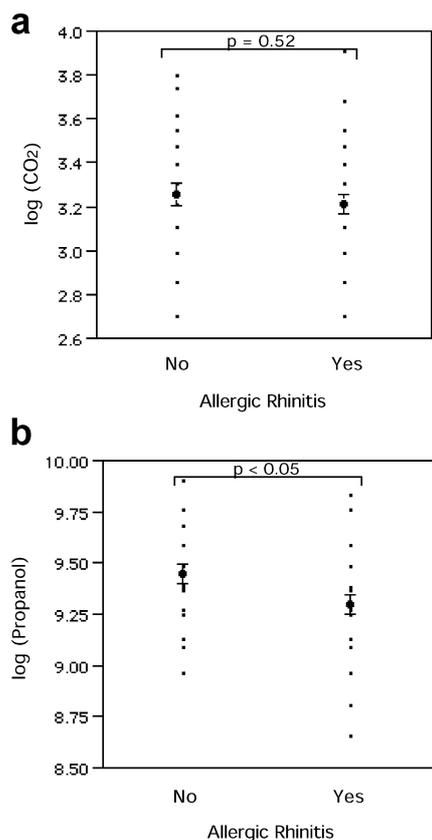
Fig. 5 a Mean ($\pm$ SEM) log CO_2 detection threshold by allergic rhinitis status (f = 0.42; P = 0.52). Number of observations exceeds number of data points due to identical observations. **b** Mean ($\pm$ SEM) log VOC localization threshold by allergic rhinitis status (f = 4.30; $P < 0.05$). Number of observations exceeds number of data points due to identical observations

more sensitive), and rhinitis status predicted VOC localization only (allergic rhinitis sufferers more sensitive). Thus, age emerged as the strongest predictor of nasal irritant sensitivity (sensory acuity), with gender and nasal allergies being weaker predictors. The magnitudes of these effects are modest, although together they explained up to 28% of the variance in CO_2 detection and 31% of the variance in VOC localization thresholds. Of the two "negative" findings (CO_2 detection vs allergies, $P = 0.52$, and VOC localization vs gender, $P = 0.10$), P values suggest that only the latter may have gained significance with a larger sample size. These observations are consistent with both epidemiological (see above) and limited experimental data published elsewhere (see Shusterman 2002 for review). Underscoring the importance of age are two more recent studies, Hummel et al. (2003) and Wysocki et al. (2003), both groups reporting age-related decrements in trigeminal performance utilizing the VOC localization task.

In our earlier study, female gender was the strongest predictor of sensory thresholds for both CO_2 detection and VOC localization (Shusterman et al. 2001). However, in that study male subjects were, on average, slightly older than female (28.5 vs 23.1 years), which

raises the question of potential confounding. Further, as there were insufficient numbers of subjects ($n = 16$) and age variability (18–40 years) to include age as an analytical variable, age effects remained to be explored. Our study examined age explicitly, by having wider inclusion criteria (18–69 years) and a larger number of subjects ($n = 60$).

In terms of test characteristics, VOC localization showed more intra-individual variability than did CO_2 detection, although when replicate determinations were averaged for a given individual, results significantly covaried between the two test systems. Methodologically, our outcomes could be influenced by such extraneous factors as consumption of hot or spicy foods, exposure to environmental pollutants, exercise, and acute allergic or infectious processes. To avoid such potential confounders we excluded smokers from the study; asked subjects to avoid eating, exercising, or using personal fragrance products prior to being tested; tested allergic rhinitic subjects outside of their allergy season, and rescheduled any subject reporting "cold" symptoms to after a 2 to 3-week symptom-free period. Potential stimulus-order effects were controlled for by the counterbalancing of testing orders within substrata of subjects.

Of note, the test compounds utilized here were presented at concentrations far in excess of those encountered in indoor environments. However, CO_2 is used here as a model (acidic) air pollutant, *not* to represent any irritant potential of low-level (500–1,000 ppm) anthropogenic CO_2 in buildings. Further, CO_2 is a widely applied test compound in nasal chemesthetic studies because it is the *only pure irritant test compound available*, permitting the utilization of temporal discrimination protocols in normosmic subjects without odor cueing. Much of the discrepancy between VOC levels used here and levels encountered in indoor air relates to *duration of exposure*. The duration of exposure during psychophysical testing is very short (i.e., 1 s). Continuous exposure in indoor settings (i.e., for hours) renders lower VOC levels irritating by a process referred to as *temporal integration* (Cometto-Muñiz and Cain 1984). [Nasal sensory irritation is distinct from odor perception, for which an opposite temporal process—adaptation—applies; (Dalton 2000).]

The biological mechanism(s) underlying these differences are largely speculative. Despite elevated symptom-reporting rates in individuals with pre-existing allergic rhinitis, aeroallergens are not thought to be responsible for the majority of symptoms in problem buildings, which suggests that rhinitis may confer non-specific sensitivity to airborne irritants (Menzies et al. 1998). In our study this association was borne out for VOC localization but not for CO_2 detection. Mechanistically, numerous biochemical mediators involved in the allergic response, including histamine, prostaglandin E_2 (PGE_2), and nerve growth factor (NGF), are known to augment the sensitivity of airway nerves to physical and chemical stimuli, a process known as neuromodulation (Ho et al.

2000; Lee and Morton 1993; Undem et al. 2000). We were careful to avoid testing during the allergy season to avoid confounding by allergen exposure, but, nevertheless, significant residual "priming" of the nasal mucosa by allergic mediators was likely present, and may have influenced neural responsiveness.

Age, the most robust predictor of chemosensory thresholds, could reduce sensitivity through a non-specific neurodegenerative process, although we have no direct evidence for such an effect. An indirect age-related mechanism is also possible, since age-related decrements in olfaction are well established, and trigeminal sensitivity has been noted to be decreased in the presence of olfactory impairment, independent of age (Gudziol et al. 2000; Hummel et al. 2003; Kendal-Reed et al. 2001; Murphy et al. 2002).

As for gender, our "positive" results for CO_2 detection are consistent with a previously published study on CO_2-induced respiratory disruption (Dunn et al. 1982) and suprathreshold scaling of CO_2 nasal irritation (Cometto-Muñiz and Noriega 1985). Further, our "negative" results for VOC localization are consistent with localization studies conducted with ethanol (Mattes and DiMeglio 2001) and with benzaldehyde and eucalyptol (Hummel et al. 2003). Why gender should affect one test system but not the other is unclear. However, we speculated that if an estrogenic influence were responsible for gender-related differences in CO_2 sensory acuity, then the association should be stronger in younger (<52 years) than in older (≥52 years) women. In fact, the failure of the gender effect to diminish with age suggests to us that an estrogenic influence on CO_2 sensory thresholds is unlikely.

Our results confirm not only that there is significant inter-individual variability in nasal trigeminal sensitivity (sensory acuity), but also that this variability is non-random in the population, generally consistent with symptom-reporting patterns in polluted (indoor) environments. Unexplored aspects of these findings include possible cross-seasonal changes in sensory acuity among seasonal allergic rhinitis sufferers, as well as underlying biological mechanisms that result in variable chemosensory sensitivity. Both issues merit further study.

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