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The Prevalence of Androstenone Anosmia

Elizabeth A. Bremner[1,2], Joel D. Mainland[1], Rehan M. Khan[1] and Noam Sobel[1,2]

[1]Helen Wills Neuroscience Institute and [2]Department of Psychology, University of California at Berkeley, Berkeley, CA 94720, USA

Correspondence to be sent to: Noam Sobel, 3210 Tolman Hall, MC 1650, University of California at Berkeley, Berkeley, CA 94720, USA. e-mail: nsobel@socrates.berkeley.edu

Abstract

It has been estimated that ~30% of the population is unable to detect the odor of androstenone. These estimates, however, were made using tests and criteria optimized for identifying detection. Such criteria favor Type II over Type I errors—that is, they are excellent at identifying true detectors at the cost of erroneously labeling some detectors as non-detectors. Because these criteria were used to identify non-detectors, it is possible that the rate of non-detection may have been overestimated. To test this we screened 55 subjects for non-detection employing previously used methods. This screen yielded nine putative non-detectors, a 16.3% putative non-detection rate. We then retested these putative non-detectors using a forced choice (yes–no) paradigm to obtain a precise measure of their sensitivity. We found that this group of putative non-detectors was significantly above chance at detecting androstenone ($P < 0.001$), despite very low self-confidence in their performance. Based on the results of the signal detection analysis in this sample, we estimate the rate of actual androstenone non-detection in young healthy adults is between 1.8 and 5.96%, which is significantly lower than previously estimated. This finding is significant considering the implications of specific anosmias on the understanding of odor discrimination.

Key words: androstenone, odor detection, specific anosmia

Introduction

Androstenone (5-androst-16-en-3-one) is a steroid considered a pheromone in boars (Patterson, 1968; Melrose *et al*., 1971), that is also present in human secretions such as saliva (Bird and Gower, 1983), sweat (Brooksbank *et al*., 1974; Claus and Alsing, 1976), and urine (Brooksbank and Haslewood, 1961). Although perceptual descriptions of androstenone odor range from 'sweaty' and 'urinous', to 'floral' and 'sweet' (Beets and Theimer, 1970; Van Toller *et al*., 1983), some individuals fail to report any olfactory percept following exposure to androstenone. Specific androstenone-anosmia, a condition where a person of otherwise normal olfactory acuity is unable to detect androstenone, has been reported at a prevalence ranging from 11 to 75% in adults (mean of men and women combined 27.5%, Table 1).

Some studies suggest a sex difference whereby androstenone anosmia is between two (Dorries *et al*., 1989) and six times (Griffiths and Patterson, 1970) more prevalent in men than in women. Such findings suggest that sex hormones may specifically influence detection rates of biologically sourced odors such as androstenone (Le Magnen, 1952), and similar odorants belonging to what Amoore and colleagues referred to as the urinous and musky primary odors (Amoore, 1977b). Also supporting a sex hormone influence on androstenone perception is the finding that the hedonics of androstenone fluctuate with the menstrual cycle. Androstenone is perceived as more unpleasant at the beginning and end of the menstrual cycle, but less unpleasant near ovulation (Hummel *et al*., 1991). However, a sex difference in androstenone detection remains controversial, as other studies reported no sex differences in detection of androstenone and related odorants (Beets and Theimer, 1970; Whissell-Buechy and Amoore, 1973; Amoore *et al*., 1975).

In turn, androstenone anosmia may have a genetic basis (Beets and Theimer, 1970; Polak, 1973; Amoore, 1977a; Wysocki and Beauchamp, 1984; Lancet, 1986; Gross-Isseroff *et al*., 1992; Lancet *et al*., 1993a,b). The ability of one monozygotic twin to detect androstenone is highly predictive of the same ability in the second twin, but this is not true for dizygotic twins (Wysocki and Beauchamp, 1984). This familial profile is in line with the theory that androstenone anosmia may be related to the expression of one or more genes encoding either a specific olfactory receptor for androstenone, or a receptor involved in a multi-receptor response to androstenone.

The estimated rate of a specific anosmia reflects a combination of the interpretation one gives to the term 'anosmia' and the statistical method used when screening for

Table 1 Studies reporting rates of androstenone non-detection[a]

Publication	Method/criterion for non-detection	Concentration	*n*	Non-detection rate (%)
(Beets and Theimer, 1970)	One trial; subjective assessment	Unknown (diluted in alcohol)	35 women, 65 men	11 (sex not specified)
(Griffiths and Patterson, 1970)	One trial; subjective assessment of smelling strip	Unknown (800 ng residual evaporated from ether as dilutant)	145 women, 165 men	7.6 women, 44.3 men
(Amoore, 1977)	2/5AFC[b] threshold; lowest conc. with both correct	2.9 ppb solution (water)	764 (sex not specified)	47 (sex not specified)
(Dorries *et al.*, 1989)	Two AFC runoff series; <5 consecutive correct	1.0×10^{-1} (highest conc.); in mineral oil	Not specified	24 females[c], 40 males[c]
(Gilbert and Wysocki, 1987; Wysocki *et al.*, 1991)	Scratch and Sniff Strip; Subjective assessment	Not specified	26 200 (sex not specified)	24 women[d], 33 men[d]
(Pause *et al.*, 1999)	2 AFC staircase; <7 reversals	1.25 mg/ml of 1,2-propanediol (highest); 0.04 μg/ml (lowest)	132 women	10.6 women
(Stevens and O'Connell, 1995)	2/5 runoff series, threshold test; <2 consecutive correct trials	5.4 mM binary dilution series, 12 steps	40 (sex not specified)	75 (sex not specified)
(Sirota *et al.*, 1999)	3AFC runoff series; <4 consecutive correct trials	1.25 mg/ml binary dilution series (mineral oil); 10 steps	20 men[e]	25 men[e]
(Morofushi *et al.*, 2000)	One/two runoff series, threshold test; <4 consecutive correct trials	5 μM–5 mM in 1.5 ml mineral oil; 10 steps	63 women	22 women
(Filsinger *et al.*, 1984)	Passive exposure; subjective assessment of impregnated paper	1 mg crystal residue evaporated from 1% solution in 100% ethanol	102 women, 98 men	9 females, 13 males
Total			27 829	27.5[f]

[a]Several major studies related to androstenone anosmia do not include information on the rate of non-detection (e.g. studies that started off with a population of non-detectors such as Wysocki *et al.*, 1989), and are thus not included in this table.

[b]AFC = alternative forced choice.

[c]Only subjects over 21 years of age were included in this average.

[d]Computed by Wysocki *et al.* on 29 200 American subjects randomly sampled from 1 221 992 respondents from the USA.

[e]Only healthy control subjects from Experiment II were included in this rate of non-detection.

[f]Mean % reported not adjusted for sample size.

it. Here we use the term anosmia as an indication of complete inability to detect the odorant (Henkin, 1966). Screening methods widely used for identifying non-detectors of androstenone have been those designed to identify odorant thresholds in detectors. The criterion in these tests is set to favor Type II over Type I errors—that is, they are excellent at identifying true detectors at the cost of erroneously labeling some detectors as non-detectors (Figure 1a). However, when seeking to identify non-detectors, one would want to err in the opposite direction, or in other words, to accurately identify true non-detectors of androstenone at the cost of erroneously labeling some non-detectors as detectors. Because the criterion for identifying detectors has been used to identify non-detectors, we predict that the rate of non-detection may have been overestimated. To test this prediction we screened for non-detectors using a 74-repetition yes–no forced choice paradigm to obtain more precise measurements of detection.

Methods

Overview

In order to identify putative non-detectors of androstenone, subjects were screened using a standard four-trial three-

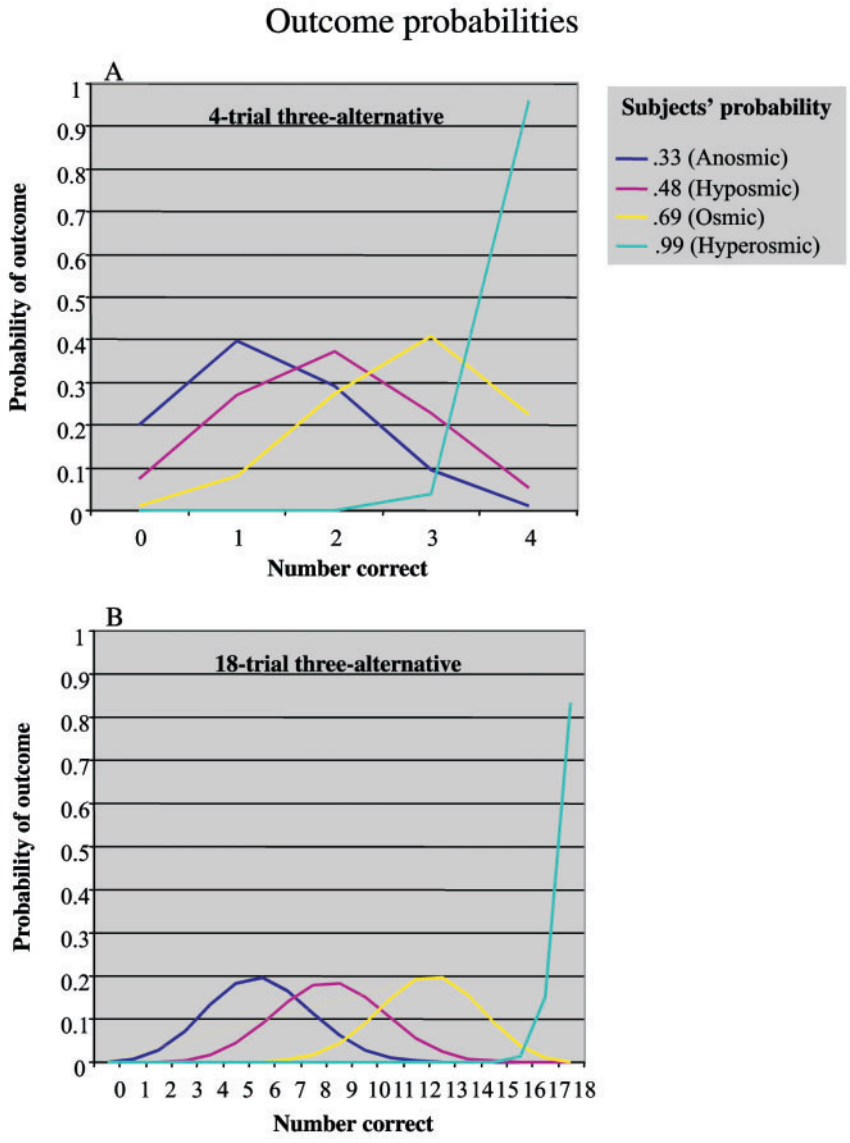

Figure 1 Outcome probabilities for three-alternative forced-choice screening. Each line depicts the probability of a particular type of person (e.g. osmic) to obtain a particular number of correct trials out of **(a)** four or **(b)** 18 repetitions. Four types of subjects are shown: anosmics who are at chance (33% accuracy), hyposmics who are slightly but significantly above chance (48% accuracy), osmics who are robustly above chance (69% accuracy), and hyperosmics who practically never miss a trial (99% accuracy). These particular four probabilities are depicted because these correspond to the major clusters in the distribution of detection. (a) Commonly used four-trial version. Using a detection criterion of four out of four correct, this is a good test for identifying detectors. As can be seen, there is less than a 6.54% chance that someone who is in fact an anosmic or hyposmic will obtain such a result. In contrast, this is a poor test and criterion for identifying anosmics, as a subject that is correct on only two of four trials may still be a detector of some sort, either hyposmic (37.38%) or osmic (27.45%). Thus, the probabilities in the four trial test are sufficient for identifying detectors but are not a strict enough test to identify true non-detectors. (b) The proposed 18 trial version for identifying non-detection. The criterion set with this test depends on the strictness merited by the particular study. Under the strictest of conditions, only those that score between two and five correct should be considered anosmics. There is only a 6.75% chance that such a person is a detector of some sort. Using such a criterion, one will falsely reject many subjects who were in fact anosmics, but this is unavoidable if one wishes to exclude hyposmics from the sample. In turn, subjects who score less than two correct on this test may be identified as malingerers.

alternative forced-choice paradigm. Considering that a more concentrated head-space may be obtained over undiluted crystal rather than over diluted androstenone, screening was performed twice, once with concentrated diluted, and once with undiluted androstenone. An additional screening protocol was performed with pyridine to assure that complete anosmics were not included in the study. Although pyridine is also trigeminal, it was used in this context in order to maintain consistency with previous studies on androstenone anosmia (Wysocki *et al.*, 1989). Subjects identified as putative non-detectors of both diluted and undiluted androstenone at screening were subsequently

invited to complete a 74-trial yes–no forced-choice detection task analyzed according to signal detection theory. As a control, a sample of subjects identified as detectors at the screening were also tested on the forced choice (yes–no) task.

Subjects

We studied 55 subjects (33 men, 22 women) ranging in age from 18 to 30 (mean = 20.5). Exclusion criteria included smoking, history of nasal or head trauma or surgery, chronic disease including allergies, current use of medication, and nasal congestion. All subjects gave informed consent to procedures approved by the UC Berkeley Committee for the Protection of Human Subjects.

Stimuli

Odorants were presented in 60 ml glass weighing jars. The undiluted stimulus consisted of 5 mg crystal androstenone (5α-androst-16-en-3-one, Steraloids Inc., Newport, RI), and the diluted stimulus consisted of 30 ml of 7.34×10^{-3} M androstenone in white light mineral oil (Sigma-Aldrich). Androstenone purity was verified with GC-MS run at a detection level of 0.5 ng contaminant/μg androstenone. The control stimulus consisted of 30 ml of 1:60 (v:v) pyridine (99%, Sigma-Aldrich) in white light mineral oil. Foils consisted of 30 ml of mineral oil for the diluted stimuli, and an empty jar for the undiluted stimulus. All jars were presented at room temperature.

Screening

Subjects were blindfolded during the task. Each trial consisted of three randomly ordered presentations, one target and two foils, such that chance performance in this task was 33% accuracy. A computer-controlled voice recording advised the participant to prepare to sniff at the tone. The computer then initiated a countdown of 3–2–1, followed by a tone. Subjects were instructed to sniff at the time of the tone, at which point they were presented with either the odorant or a foil. Following three successive presentations with an inter-stimulus interval (ISI) of 7 s, subjects were prompted by the computer to identify which jar had contained the odorant (a, b or c), and to specify their confidence in their response on a scale of 1–10, with 1 being a guess and 10 being most certain. Following their answer, subjects were given computer-generated feedback that indicated whether they were correct or not and informed them which jar had in fact contained the odorant. There was a 45 s inter-trial interval (ITI) in order to minimize adaptation effects. The above combination of blindfolding and computer–subject interactions was designed to prevent any experimenter-generated cues as to presentation content.

Subjects completed four trials per odorant. Strict criteria were used to define putative androstenone non-detectors. Subjects that were correct on three or more trials of either diluted or undiluted androstenone were considered detectors and excluded. Subjects were considered putative non-detectors if they were wrong on three or more trials of both diluted and undiluted androstenone (25% accuracy or less). Those subjects who were correct on two trials of either diluted or undiluted androstenone were given two extra trials, bringing the total trials in that screen to six. If they were wrong on both additional trials (33% accuracy, which is chance), they were included, but if they were correct on either additional trial they were defined as detectors and excluded.

Yes–no forced-choice detection

Subjects deemed putative non-detectors by the screening task were entered into the yes–no forced-choice detection task. The task was performed with undiluted androstenone. Methods were identical to those at screening, except that instead of three alternatives, trials consisted of one presentation of either androstenone or a foil presented in a random order (ISI = ITI = 45 s) such that chance performance on this task was 50% accuracy. The subject indicated whether the odor was present (yes) or not (no), but did not receive any feedback. The task consisted of 74 such trials. In addition to percentage accuracy, a signal detection analysis was performed on the results of the yes–no forced-choice detection task, computing d', a measure of sensitivity, and β, a measure of bias (Green and Swets, 1966).

Results

Screening

All subjects accurately detected all trials of pyridine. Of the 55 subjects screened, 46 were determined to be detectors of androstenone, having successfully detected diluted androstenone, undiluted androstenone, or both. Detection was better for undiluted versus diluted androstenone. Of the 46 detectors, 12 failed to detect androstenone diluted in mineral oil despite detection of undiluted androstenone, but only two failed to detect undiluted androstenone despite detection of diluted androstenone. A total of nine subjects (six men, three women) failed to detect both diluted and undiluted androstenone, and were considered putative non-detectors to be entered into the yes–no forced-choice study. Of these nine putative non-detectors, six failed three of the four trials, and three initially failed two of four trials, but also failed the two additional verification trials (i.e. failed four of six trials in total). The 16.3% non-detection rate obtained here was lower than values previously reported in the literature (Table 1), indicating that we were relatively strict in our criteria. These putative non-detectors formed 18.1% of the men and 13.6% of the women that participated in the study, suggesting no significant sex difference in the current results ($Z = 0.457$, $P = 0.65$).

Analysis of confidence ratings showed that whereas detectors reported higher confidence ratings following correct versus incorrect detection of undiluted androsten-

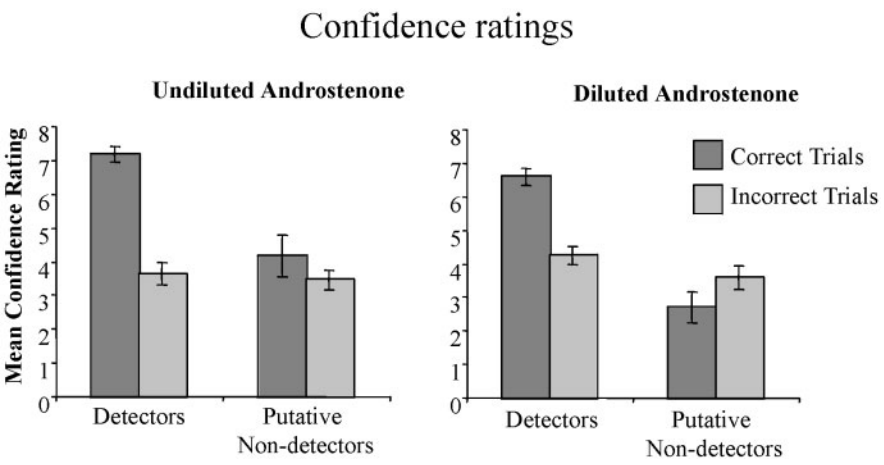

Figure 2 Confidence ratings made by detectors and putative non-detectors on correct and incorrect trials of detecting undiluted and diluted-yet-concentrated androstenone. Whereas detectors were significantly more confident when correct versus incorrect, putative non-detectors were equally confident when correct versus incorrect. Furthermore, when correct, detectors were more confident than putative non-detectors, but not when incorrect (statistics in results section). These results suggest a difference between detectors and putative non-detectors at the perceptual level.

one [mean correct = 7.19, mean incorrect = 3.65; $t(45)$ = 8.82, $P < 0.001$], putative non-detectors were equally confident whether they were correct or incorrect [mean correct = 4.17, mean incorrect = 3.46; $t(8) = 1.04$, $P = 0.32$]. Two-factor analysis of variance (ANOVA) was conducted on the confidence ratings for the diluted and the undiluted androstenone using type of subject (detectors versus putative non-detectors) and trial type (correct versus incorrect) as factors. Significant interaction terms were obtained for both the undiluted [$F(1,242) = 10.32$, $P < 0.0016$] and diluted [$F(1,252) = 7.98$, $P < 0.0052$] androstenone. Figure 2 shows the means and standard errors for the interaction. *Post hoc* *t*-tests revealed that detectors reported higher confidence following correct detection [mean correct = 7.19, mean incorrect = 3.65; $t(45) = 8.82$, $P \leq 0.001$], putative non-detectors were equally confident whether they were correct or incorrect [mean correct = 4.17, mean incorrect = 3.46; $t(8) = 1.04$, $P = 0.32$)]. The same pattern was observed with the undiluted androstenone so that putative non-detectors were significantly less confident than detectors following correct trials [mean non-detectors = 4.17, mean detectors = 7.19; $t(52) = 4.65$, $P < 0.001$)], but equally confident following incorrect trials [mean non-detectors = 3.46, mean detectors = 3.65; $t(52) = 0.42$, $P = 0.68$]. These results are robust using a Bonferroni correction which for four tests sets the per test level of significance at 0.013 for an overall 0.05 level of significance.

Yes–no forced-choice task

One subject discontinued participation due to increasing nasal congestion during task performance. Mean accuracy for the remaining eight subjects was 57.5 ± 2.4% (Table 2). This group deviation from chance was significant as evidenced in the overall positive d' (mean $d' = 0.42$ (±0.13), $t(7) = 3.17$; $P < 0.016$). An alternative, non-parametric sign test on the percent correct values confirms this result. Under the null hypothesis non-detectors should be at chance (50%) on average and equally likely to have a percent correct score higher or lower than chance. Only one subject (SD028) obtained a percent correct score below chance on the extended yes–no forced choice task, indicating that the putative non-detectors tended to score significantly better than chance (binomial $P < 0.036$). In other words, the results of the comprehensive task analyzed by measures of signal detection were very different from the results of the screen, and suggested that the group of putative non-detectors were in fact detectors (Figure 3). It is important to note that these tests allow us to conclude that the group of putative non-detectors as a whole perform better than chance, but do not allow us to determine how much each individual within this group differs from chance. To answer this question with sufficient power would require a large number of simple forced choice (yes–no) trials and was beyond the scope of the present study.

Table 2 Putative non-detectors at signal detection

Subject	Sex	d'	β	% correct
SD003	M	1.224	0.633	72
SD005	M	0.415	1.074	58
SD018	M	0.340	1.000	57
SD027	M	0.372	1.171	57
SD028	F	–0.103	0.998	47
SD036	F	0.312	1.017	55
SD053	M	0.275	1.048	55
SD056	M	0.498	1.151	59

Performance of the eight putative non-detectors at the signal detection task where chance is 50% accuracy. Only one subject (SD028) was below chance and obtained a negative d' score.

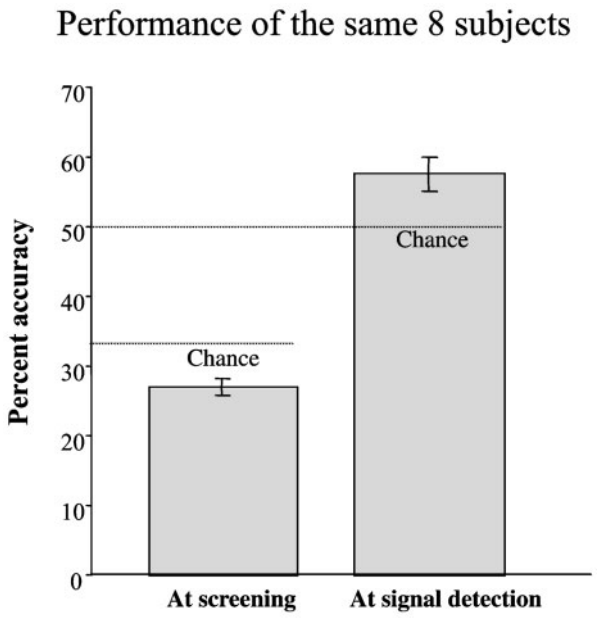

Figure 3 Performance of eight putative non-detectors at the screening task and at the signal detection task. Chance performance is 33% accuracy at screening and 50% at signal detection. This figure plainly illustrates the main finding of this study whereby subjects deemed non-detectors at a screening task consisting of only four trials may in fact be detectors as revealed in the 74 trial task.

To test for a difference in bias between detectors and putative non-detectors, one would need to compare β scores for these populations. To this end we administered the 74-trial yes–no forced-choice task to 20 subjects randomly selected from those deemed detectors at screening. The distribution of scores for this group was bimodal with 11 subjects never missing a single trial over 74 presentations (hyperosmics), and the remaining subjects clustering around a d' of 1.93 [osmics, difference from chance, $t(8) = 6.99$, $P < 0.001$]. There was a weak trend towards lower β scores in putative non-detectors [mean non-detectors = 1, mean detectors = 2.5, $t(15) = 1.96$, $P = 0.068$] indicating a trend for non-detectors to be more tolerant of false alarms than were detectors.

To estimate the rate of androstenone non-detection in the general population we examined the make up of our entire sample of 55 subjects that clustered into four groups: anosmics—the one subject with a negative d', hyposmics—subjects who were slightly but significantly above chance, osmics—subjects robustly above chance, and hyperosmics—subjects that essentially never fail to detect androstenone (Figure 4). We treated osmics and hyposmics as derived from a single underlying distribution of sensitivity so that we could estimate the rate of non-detection in the overall population. The mean d' of this distribution was 1.216 (SD = 1.01). Based on a normal distribution with this mean and standard deviation, one would expect a non-detection rate ($d' < 0$) of 11.43% among osmics and hyposmics. As this

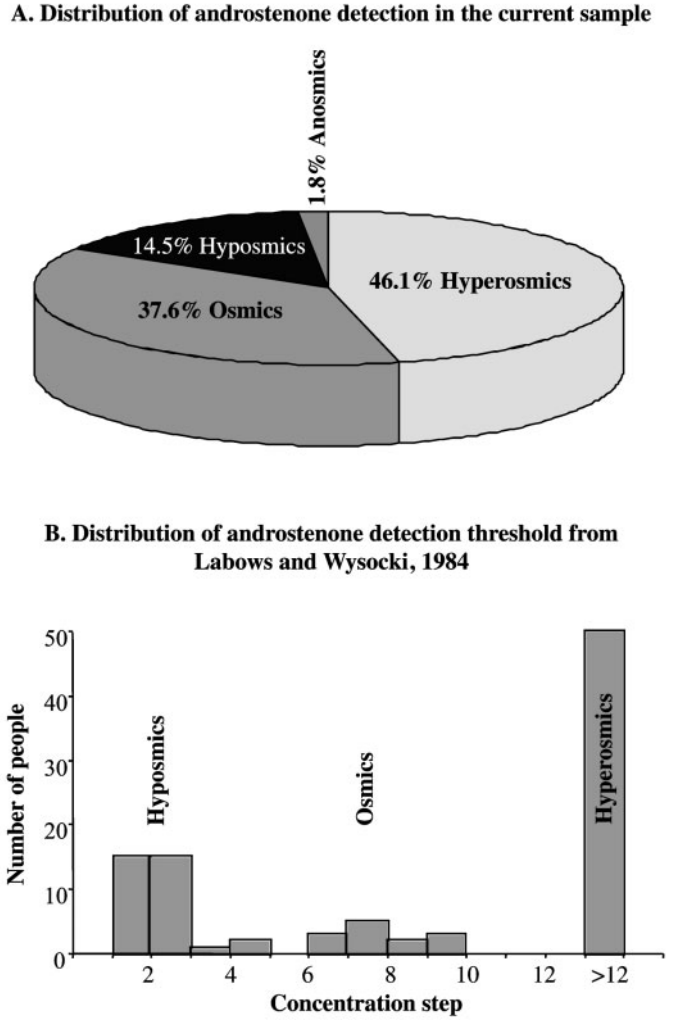

Figure 4 Distribution of androstenone detection. **(A)** Detection at the signal detection task where chance was 50% accuracy. Hyperosmics, who comprised 46.1% of the sample, were at ~100% accuracy where d' is undefined. Osmics, who comprised 37.6% of the sample, were at ~80% accuracy where d' is ~1.9. Hyposmics, who comprised 14.5% of the sample, were at ~59% accuracy where d' is ~0.49. anosmics, who comprised 1.8% of the sample, were at 47% accuracy where d' is –0.1. **(B)** Adapted from figure 2 in (Labows and Wysocki, 1984). The suggested labeling of the clusters in (B) was added here by us to point to the overlap between our and their results. The added contribution of the current result is in quantifying the very small group of absolute non-detectors that are revealed only with high sampling such as that offered by the 74-trial yes–no forced-choice task.

group comprises 52% of the sample, we would expect a 5.96% non-detection rate in the overall population. This analysis did not consider the hyperosmics because d' is undefined in cases where subjects made no errors. A second estimate of the overall rate of non-detection that considers the hyperosmics as well is obtained by abandoning the assumption of a normal distribution, and observing that only one of the 55 subjects had a d' score less than zero. This ratio predicts a 1.8% non-detection rate in the general

population. Thus we predict a population non-detection rate between 1.8 and 5.96%.

Discussion

The current findings suggest that the prevalence of androstenone anosmia is significantly lower than previously estimated. Several statistical methods have been employed to characterize olfactory detection and threshold (Cometto-Muniz and Cain, 1990, 1998; Kurtz *et al*., 1999; Linschoten *et al*., 2001; Cometto-Muniz *et al*., 2002) that could also be used to identify non-detection as long as the correct criterion is applied. Here we used such a test and criterion and found that definite non-detection of androstenone is in fact quite rare. The current results do not point to a sex difference in androstenone anosmia, but considering that this study was not designed to specifically address that question, we do not consider this null finding conclusive. A concern in the design of this study was that if we were lenient in comparison to previous studies at defining putative non-detectors at screening, it would be no surprise that a stricter test would later reveal they were in fact detectors. This concern was addressed by screening with feedback for both diluted and undiluted androstenone, and by ruling on the statistically strict side of employing the commonly used three-alternative forced-choice task at screening. This combination yielded a 16.3% putative non-detection rate. This rate is lower than the commonly reported rate (Table 1), making it safe to predict that subjects labeled here as putative non-detectors at screening were highly likely to have received the label of non-detector in previous studies. Nevertheless, these putative non-detectors could detect androstenone at above chance level as indicated by the signal detection analysis ($P < 0.001$).

In graphing the distribution of androstenone detection thresholds, Labows and Wysocki (Labows and Wysocki, 1984) depicted three clusters that overlap with four clusters seen here. One cluster, hyperosmics, scored 12 and higher on their binary dilution scale. This cluster corresponds to a group consisting of 46.1% of the current sample that was at 100% accuracy on the yes–no task (undefined d'), i.e. never failed to detect a single trial over 74 repetitions. A second group, osmics, scored ~8 on their binary dilution scale. This cluster corresponds to a group consisting of 37.6% of the current sample that were at 80% accuracy and had d' scores near two. A third group, specific hyposmics, scored ~2 on their binary dilution scale. This cluster corresponds to a group consisting of 14.5% of the current sample that were at 59% accuracy and had d' scores that were only slightly but significantly above zero. Finally, here we used signal detection to also isolate the fourth and very small group of true specific anosmics consisting of 1.8% of the sample (one subject) that was at 47% accuracy and had a negative d' score (Figure 4).

The rarity of specific anosmia to androstenone is significant in light of the implications of specific anosmias on the understanding of odor discrimination (Guillot, 1948; Amoore, 1967; Wysocki *et al*., 1977; Lancet *et al*., 1993a,b; Griff and Reed, 1995; Zhang and Firestein, 2002). Models of odor discrimination that take specific anosmias into account mostly suggest that these anosmias are related to a specific make-up of genes encoding for specific olfactory receptors. In the simplest form, one may suggest that a person selectively anosmic to androstenone may be missing a putative androstenone receptor. Based on this assumption of genetic polymorphism one may aim to isolate the putative androstenone receptor gene by screening for androstenone anosmia and comparing gene expression between osmics and anosmics. The current findings, however, suggest that most subjects considered specific anosmics may in fact be specific hyposmics. Thus, hypotheses derived under the assumptions of complete non-detection or anosmia may be misleading. The current results, however, do not rule out specific androstenone hyposmia as a helpful key toward elucidating the genetic basis of odor discrimination. Even under the assumption that most seemingly anosmics are in fact hyposmics, one may suggest that such hyposmia reflects a specific genetic make up. Under the assumption of a single putative androstenone receptor, one may suggest that at exceedingly high concentrations such as those used here, androstenone will saturate and activate other receptors that would ordinarily not respond to androstenone at lower concentrations. Thus, androstenone hyposmia may still reflect complete lack of a putative androstenone receptor. In turn, under the assumption of a multi-receptor response to androstenone, androstenone hyposmia may reflect a missing component of a complex response, and may therefore contain helpful cues towards understanding the genetics of olfactory perception.

Hyposmia as a clue to the genetics of odor discrimination inherently assumes that hyposmia is related to peripheral mechanisms, namely total lack of, or a reduced number/density of particular olfactory receptors. An alternative view is that specific hyposmia is the result of a central mechanism. In other words, that the input from the nose to the brain may be similar across osmics and hyposmics, but hyposmics fail to process this signal as an olfactory percept. This distinction may be related to that made between an early preconscious stimulus decoding phase, and a later phase reflecting conscious stimulus evaluation, as evidenced in temporally distinct olfactory event-related potentials (Pause *et al*., 1999). There are several lines of evidence pointing to a peripheral odor response that does not always translate into odor awareness, a phenomenon described as 'blindsmell' (Sobel *et al*., 1999) [not to be confused with 'odor blindness', a term coined by Amoore *et al*. (Amoore *et al*., 1968) to describe specific anosmia]. For example, conditioning with undetected odors can induce negative mood (Kirk-Smith *et al*., 1983), and undetected odors can affect patterns of EEG (Lorig *et al*., 1990; Schwartz *et al*.,

1994), galvanic skin response (Van Toller *et al.*, 1983), and brain activation as measured with both functional magnetic resonance imaging (Sobel *et al.*, 1999) and positron emission tomography (Jacob *et al.*, 2001). In the current study, although hyposmics had no percept of the odorant (Figure 2), they could detect its presence at above chance levels (Table 2). Finally, Schiffman reported that hypnosis can induce detection at levels not obtained in the normal wake state (Schiffman, 1979). Considering it is unlikely that hypnosis alters gene expression at the olfactory epithelium, this finding further implicates a central mech- anism that blocks conscious olfactory detection. Although we favor the hypothesis that implicates the central late rather than peripheral early processing phase for selective androstenone hyposmia, the current data do not preferentially support the peripheral or central hypothesis. Furthermore, the reasons for androstenone hyposmia may be different from those for complete androstenone anosmia, and whereas a central mechanism may be responsible for the former, a peripheral mechanism may be responsible for the latter. The contribution of the current study is in pointing to the rarity of such complete androstenone anosmia. Finally, a word of caution may be merited as to the pathway by which the hyposmics here detected androstenone. Although we know of no evidence for trigeminal responses to this compound, this alternative is not ruled out. Thus, trigeminal responses to androstenone may complicate even further any deduction from the olfactory phenotype to genotype.

An additional question is how our findings impact on the interpretation of androstenone learning studies. Wysocki *et al.* (Wysocki *et al.*, 1989) first described this phenomenon wherein individuals unable to detect androstenone acquire the ability to detect it following systematic exposure. This phenomenon has been replicated in an animal model (Wang *et al.*, 1993) and in humans (Stevens and O'Connell, 1995; Moller *et al.*, 1999; Pause *et al.*, 1999), as well as with other odorants (Dalton *et al.*, 2002; Cain and Schmidt, 2002), and may be considered a model for adult neural plasticity. Regardless of whether the underlying plasticity is central (Brennan and Keverne, 1997; Mainland *et al.*, 2002) or peripheral (Wang *et al.*, 1993; Yee and Wysocki, 2001), the current findings imply a slight reframing of this result. Whereas previously it was thought that androstenone exposure led to a shift from complete non-detection to detection, our findings imply the shift may have been from poor detection to better detection. Furthermore, not all subjects become sensitized in androstenone learning studies. It is tempting, therefore, to speculate that hyposmics (those that appear non-detectors at a standard screen, but are above chance at signal detection) can develop sensitivity, but absolute anosmics can not. (Testing this hypothesis, however, is a daunting task. Considering that true anosmics may constitute only 1.8% of the population, one would have to screen 1111 subjects to obtain a sample of 20 true androstenone anosmics.) Regardless, however, of whether the shift in previous studies was from non-detection to detection, or poor detection to better detection, this phenomenon remains equally worthy and intriguing as a model for plasticity in the adult human olfactory system.

Determining that the group of putative non-detectors obtained at screening was comprised primarily of hyposmics who were significantly above chance was straightforward. In turn, there are several avenues by which one may estimate the rate of non-detection in the general population based on these results. Taking a nonparametric approach and directly extrapolating from the current d' scores to the general population, one would estimate a 1.8% rate of non-detection. In turn, if one were to assume that these d' scores reflected a normal distribution of d' scores in the general population, one would estimate a 5.96% overall rate of non-detection. Although we find the former, lower of these two values, to be the appropriate estimate, we venture on the conservative side of concluding that the prevalence of androstenone non-detection (complete specific anosmia) in young healthy adults is between 1.8 and 5.96%.

Finally, one may ask what method should be used to screen for non-detectors. As a rule, longer tests containing increased sampling promise higher accuracy (Doty *et al.*, 1995). The 74-trial yes–no forced-choice task with a 45 s ISI that we used here is robust at identifying true non-detectors, but takes nearly 90 min to complete, and is thus not well suited for scenarios where one needs a quick screen for non-detection. As a compromise, based on the distribution of d' scores in this study, we conclude in recommending an 18-trial three-alternative forced choice paradigm with a 45 s ISI that takes ~20 min to conduct. Chance at this screen is six correct. If a particular study calls for strict criteria of non-detection, we recommend identifying as non-detectors those who score between two and five correct, thus accepting only a 6.75% chance of erroneously including hyposmics at the cost of a 58.3% chance of erroneously rejecting anosmics (Figure 1b). In cases where one can afford more lenient criteria that will combine ansomics and hyposmics, we recommend selecting those who score between two and nine correct, thus accepting a 65.78% chance of erroneously including hyposmics at the cost of a 4.78% chance of erroneously rejecting anosmics.

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