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Main Article

Olfactory clearance: what time is needed in clinical practice?

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Abstract

Objective: To determine olfactory adaptation and clearance times for healthy individuals, and to assess the effect of common variables upon these parameters.

Study design and setting: Fourteen healthy volunteers were recruited for a series of tests. Their initial olfactory threshold levels for phenethyl alcohol were determined. After olfactory exposure to a saturated solution of phenethyl alcohol (i.e. olfactory adaptation), the time taken for subjects to return to their initial olfactory threshold was then recorded (i.e. olfactory clearance). Visual analogue scale scores for subjective variables were also recorded.

Results: The 14 subjects performed 120 tests in total. Despite consistent linear trends within individuals, olfactory clearance times varied widely within and between individuals. The mean olfactory clearance time for phenethyl alcohol was 170 seconds (range 81–750). Univariate analysis showed a relationship between olfactory clearance times and age ($p = 0.031$), symptoms ($p = 0.029$) and mood ($p = 0.048$).

Conclusions: When testing a person's sense of smell in a clinical setting, recent exposure to similar smells should be noted, and a period of 15 minutes needs to be allowed before retesting if using phenethyl alcohol. Other variables need not be controlled, but greater clearance time may be needed for older patients.

Key words: Olfaction; Physiological Adaptation

Introduction

Olfaction may be phylogenetically the oldest sense that humans possess, yet it remains the least understood of all our senses, despite the fact that olfactory disturbances are common complaints in the general population.[1] This relative lack of understanding, compared with knowledge regarding vision or hearing, is partly due to the very subjective nature of this sensory modality. Psychometrics play a large part in the process of olfaction,[2] but there are also infinite combinations of odours which can be detected. The exact 'smell map' remains to be defined, although there have been attempts to realise this 'visualisation' of olfaction.[3,4]

Adaptation is a common feature of all sensory modalities.[5] Odour adaptation has been referred to as 'the ability of the olfactory system to adjust its sensitivity at different stimulus intensities'.[6] Olfactory adaptation is a time-dependent, reversible reduction in sensitivity due to prior odour exposure, or during steady stimulation with odours.[6] Adaptation in olfaction allows the olfactory system to maintain equilibrium with the odourant concentrations in the ambient environment, yet respond to the appearance of novel odours or changes in odourant concentration.[5] Reductions in sensory system responses to stimuli may occur throughout the sensory pathway,[7] from olfactory receptors,[8] through olfactory second order neurones,[9,10] to olfactory primary and higher order cortical areas.[11,12] Recovery will likewise occur throughout the pathway.

This study attempted to quantify olfactory adaptation and clearance times in the presence of a saturated solution, in a number of human volunteers, in order to determine whether these times were consistent within and between individuals. Our hypothesis was that intra-subject variance would be low. Recovery times are important when assessing a subject's sense of smell. For example, during otorhinolaryngological assessment, when presenting an individual with a particular odour, how long should the patient be allowed to rest before the odour is presented again? Although previous studies have assessed adaptation times for odours,[13] to date no published study appears to have demonstrated

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olfactory clearance times for phenethyl alcohol in humans.

Methods

Full ethical approval from a regional ethics committee was obtained prior to commencement.

Fourteen healthy volunteers were recruited, both men and women, with an age range of 22 to 61 years. Information was recorded regarding smoking status, previous nasal problems, past medical history and current medication. Information was also obtained upon each visit regarding exposure to strong smells within the previous 48 hours, and the presence of upper respiratory tract symptoms. Visual analogue scores were used to record each individual's perceived sense of smell, nasal symptoms, tiredness and mood.

Peak inspiratory nasal flow was recorded using a Youlton peak flow meter (Clement Clarke, Harlow, UK), and temperature and humidity were recorded with a thermohygrometer (Fisher Scientific, Loughborough, UK).[14] The nose was examined using a Thudicum's speculum and light source.

Initial thresholds were determined using 3 ml dilutions of phenethyl alcohol in mineral oil,[15] which were placed in small, stoppered, 28 ml glass bottles (VWR International, Lutterworth, UK), with concentrations ranging from 10^{-9} (log vol/vol) (least concentrated) to -10^{-2} (most concentrated). Individuals were then asked when they could detect phenethyl alcohol, on being presented with sequentially stronger concentrations from weakest to strongest, using an ascending technique.[16] Air was passed through a Buckner flask containing a saturated solution of phenethyl alcohol, which was then presented via a facemask at a flow rate of 3 l per minute. A saturated solution was used, as it was found that individuals took much longer to adapt to weaker solutions. The time taken for individuals to be unable to smell phenethyl alcohol at concentrations of 1 per cent (10^{-2}) was recorded in seconds. Once an individual was unable to smell phenethyl alcohol at 10^{-2}, the pump was stopped, and the time taken for the subject's olfactory detection of phenethyl alcohol to return was recorded by alternating a few breaths of fresh air with a sniff of the glass vials containing phenethyl alcohol, starting at 10^{-2} and working back to the subject's original threshold (and beyond if an individual was able, in half log steps). This process was repeated on 10 separate occasions, with readings separated by a minimum of 48 hours (four subjects did not perform all 10 tests – see Results section).

The time taken (in seconds; *y* axis) was plotted against the olfactory threshold measured in logarithmic steps from 10^{-2} to the lowest threshold detected (*x* axis), using Axum (Adept Scientific, Letchworth, UK). A best-fit line was drawn using linear least squares, and the gradient was recorded, representing the time taken in seconds for each clearance interval (i.e. the time taken for olfactory detection of phenethyl alcohol to return by one logarithmic interval). The results were otherwise analysed using Stata software (Stata SE for Windows Version 9.1, Statacorp LP, College Station, Texas, USA).

Results

Fourteen volunteers were recruited, eight women and six men. Ten subjects (six women and four men) completed 10 sets of data; two women completed nine and five sets of data, variously, and two men completed only three data sets. The mean age of the group was 39.1 years. Seven subjects were nonsmokers, four were smokers and three were ex-smokers.

Initial olfactory thresholds

Due to the non-normal distribution, the bootstrap algorithm based on 1000 iterations was used to derive *p* values and confidence intervals (CIs) from the linear mixed model. The initial olfactory thresholds did not show any significant relationship to any of the variables examined (Table I); the distribution of the initial olfactory thresholds is seen in Figure 1, with a mean value of $10^{-4.739}$ log vol/vol (range 10^{-3}–10^{-8}).

Olfactory adaptation times

The mean time required for olfactory adaptation to phenethyl alcohol to occur was 157.7 seconds (range 29 to 721). Due to the non-normal distribution, the bootstrap algorithm based on 1000 iterations was used to derive *p* values and CIs from the linear mixed model. Univariate analysis of these variables revealed that only nasal symptoms, as documented using visual analogue scale (VAS) scores, had a relationship with adaptation time ($\beta = -14.01$, $p < 0.026$; Table II, Figure 2). This meant that an increase of one VAS unit in reported symptoms reduced the time to adaptation by 14 seconds (95 per cent confidence interval −26 to −1.7). There was no significant relationship between the initial olfactory threshold and the olfactory adaptation time. An example of olfactory adaptation times for one subject is displayed in Figure 3.

TABLE I

RELATIONSHIP OF RECORDED VARIABLES TO INITIAL OLFACTORY THRESHOLDS

Variable	Estimate*	95%CIs	*p*
Age	−0.01	−0.03 to 0.01	0.434
Smell	−0.16	−0.33 to 0.00	0.056
Symptoms	−0.04	−0.09 to 0.01	0.121
Mood	−0.07	−0.21 to 0.06	0.291
Tiredness	−0.02	−0.08 to 0.04	0.519
Temperature	−0.05	−0.12 to 0.02	0.186
Humidity	0.00	−0.01 to 0.01	0.870
PINF	0.00	−0.01 to 0.01	0.883
Sex (female *vs* male)	−0.08	−0.68 to 0.53	0.803
Smoker			0.750
– Current *vs* non	−0.05	−0.90 to 0.81	0.913
– Ex *vs* non	0.19	−0.35 to 0.72	0.497

*Estimated increase in initial olfactory threshold due to a unit change in the variable. CI = confidence interval; PINF = peak inspiratory nasal flow; non = non-smoker; ex = ex-smoker

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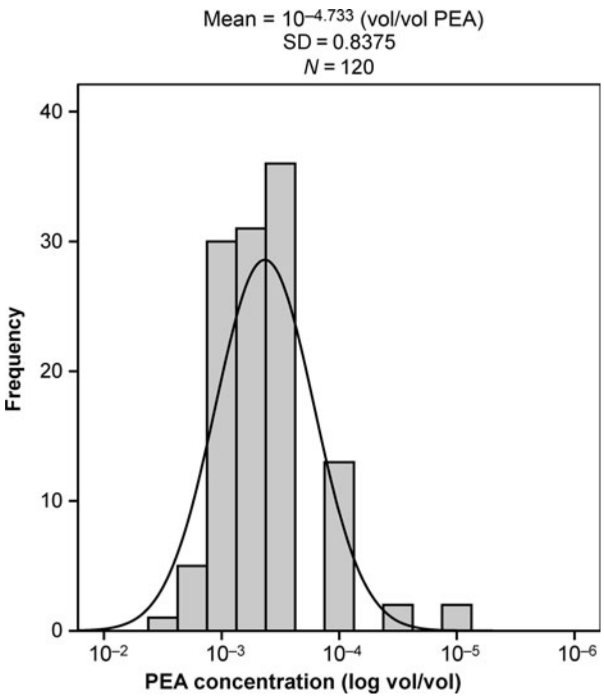

FIG. 1

Initial olfactory thresholds. SD = standard deviation

Olfactory clearance times

The mean olfactory clearance time for phenethyl alcohol was 170 seconds (range 81–750). Again, due to the non-normal distribution, the bootstrap algorithm based on 1000 iterations was used to derive p values and CIs from the linear mixed model. Univariate analysis of the variables showed a relationship with age ($p = 0.031$) and mood ($p = 0.029$) see figure 4; however, in a multivariate model (not shown), neither of these variables were significant (Table III). An example of olfactory clearance times for one subject is displayed in Figure 5. The influence of the variables on clearance time meant that for each yearly increase in age, the clearance time increased by 3.94 seconds (95 per cent CI 0.35–7.52), and for each one-unit increase in VAS mood score (i.e. worsening mood), the clearance time decreased by 14.42 seconds (95 per cent CI 0.10–28.73).

TABLE II

RELATIONSHIP OF RECORDED VARIABLES TO OLFACTORY ADAPTATION TIMES

Variable	Estimate*	95%CIs	p
Initial threshold	11.52	−4.77 to 27.82	0.166
Age	1.27	−1.35 to 3.89	0.343
Smell	−8.70	−17.98 to 0.58	0.066
Symptoms	−14.01	−26.33 to −1.70	0.026
Mood	−2.10	−14.30 to 10.09	0.735
Tiredness	−2.60	−11.49 to 6.28	0.566
Temperature	2.52	−1.72 to 6.77	0.244
Humidity	0.54	−0.57 to 1.66	0.340
PINF	0.32	−0.09 to 0.74	0.129
Sex (female *vs* male)	−26.32	−92.19 to 39.54	0.434
Smoker			0.953
– Current *vs* non	−7.84	−89.26 to 73.58	0.850
– Ex *vs* non	7.26	−93.88 to 108.40	0.888

*Estimated increase in initial olfactory threshold due to a unit change in the variable. CI = confidence interval; PINF = peak inspiratory nasal flow; non = non-smoker; ex = ex-smoker

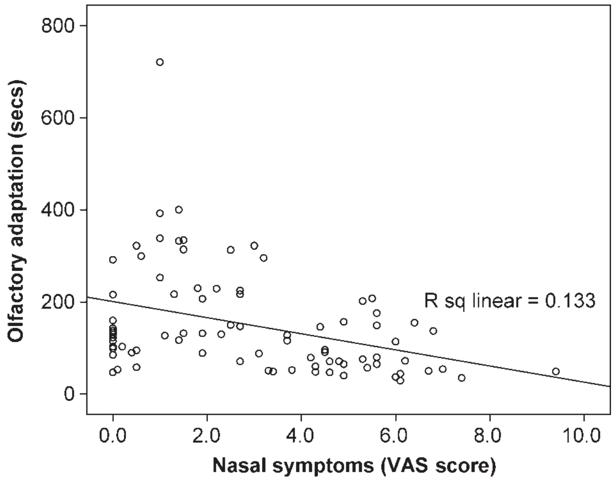

FIG. 2

Severity of nasal symptoms (expressed as visual analogue scale (VAS) scores) versus olfactory adaptation time. Secs = seconds

Analysis of the olfactory clearance curves revealed an average gradient of 133.24 (standard deviation = 89.64, minimum = 16.383, maximum = 443). Olfactory clearance significantly differed between individuals ($p < 0.0001$), based on a log-transformed analysis of variance (Table IV). The within-subject variation was estimated at 0.5 (on the log-transformed scale), so that the 95 per cent CI for the slope is, on the original scale, by 39.08 to 273.77 seconds.

Relationship of olfactory adaptation times to olfactory clearance times

We used a linear mixed model with time to olfactory adaptation as the independent variable and time to olfactory clearance as the dependent variable. Once again, due to the non-normal distribution, the bootstrap algorithm based on 1000 iterations was used

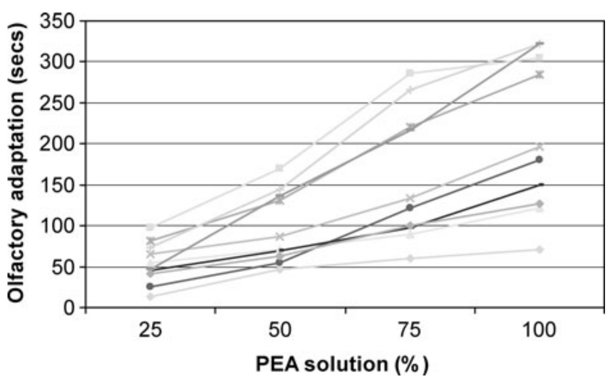

FIG. 3

Olfactory adaptation times for subject 1. Different symbols plot different adaptation times on separate occasions. PEA = phenethyl alcohol

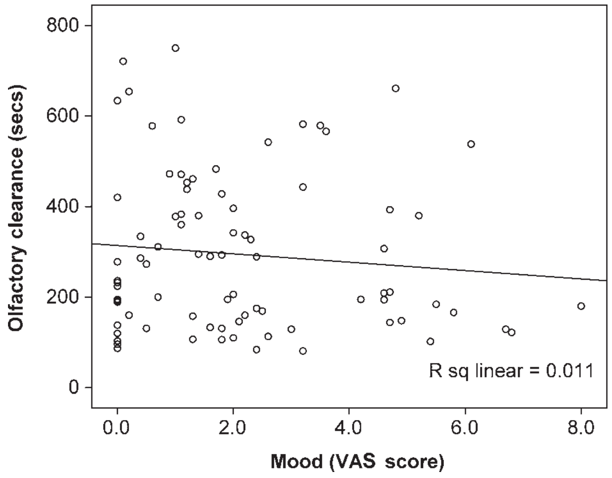

FIG. 4

Worsening mood (expressed as visual analogue scale (VAS) score) versus olfactory clearance time. Secs = seconds

TABLE III

RELATIONSHIP OF RECORDED VARIABLES TO OLFACTORY CLEARANCE TIMES

Variable	Estimate*	95%CIs	p
Initial threshold	−2.21	−59.30 to 54.88	0.940
Age	3.94	0.35 to 7.52	0.031
Smell	8.68	−16.95 to 34.30	0.507
Symptoms	5.19	−8.53 to 18.91	0.458
Mood	−14.42	−28.73 to −0.10	0.048
Tiredness	−2.44	−11.62 to 6.73	0.602
Temperature	6.31	−10.33 to 22.95	0.457
Humidity	−0.77	−2.15 to 0.61	0.274
PINF	0.98	−0.10 to 2.06	0.077
Sex (female *vs* male)	−85.81	−189.64 to 18.03	0.105
Smoker			0.2951
– Current *vs* non	93.43	−23.78 to 210.64	0.118
– Ex *vs* non	49.15	−123.02 to 221.32	0.576

*Estimated increase in initial olfactory threshold due to a unit change in the variable. CI = confidence interval; PINF = peak inspiratory nasal flow; non = non-smoker; ex = ex-smoker

to derive p values and CIs; this analysis revealed no evidence of a relationship between olfactory adaptation time and clearance time ($p = 0.353$, 95 per cent CI −0.19–0.54). A comparison of olfactory adaptation times to clearance times showed a mean difference of 149 seconds (95 per cent CI 119–179, $p < 0.0001$), using a paired t-test.

Variation within and between subjects

The intra-class correlation coefficient was used as a measure of reliability. The intra-class correlation coefficient for olfactory clearance time was 47 per cent (95 per cent CI 24–71 per cent) and for olfactory adaptation time was 61 per cent (95 per cent CI 39–82 per cent). That is to say that 47 per cent of the variation in clearance times was due to variation between subjects.

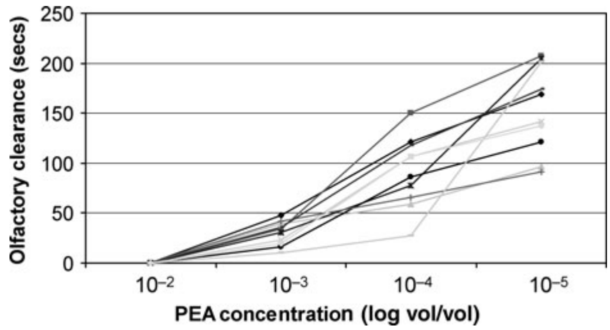

FIG. 5

Olfactory clearance times for subject 2. Different symbols plot different clearance times on separate occasions.

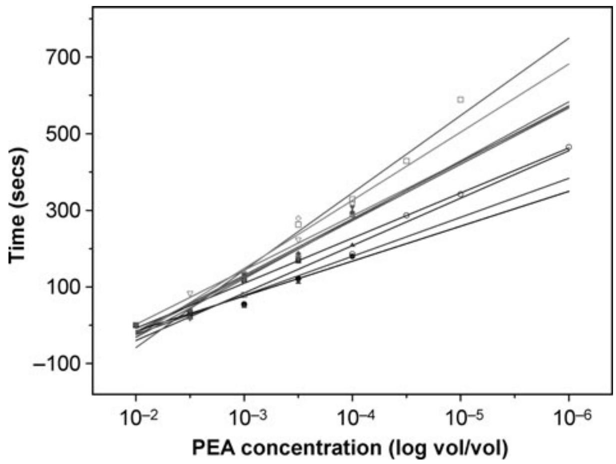

FIG. 6

Olfactory clearance curves for subject 3. Different clearance curves for one individual.

Discussion

Olfactory clearance times showed large variations between and within subjects, with the intra-class correlation coefficient results indicating that subjects were less consistent within themselves, as compared with other subjects, and took longer on average to clear than to adapt. The time constant for olfactory adaptation is not easy to determine, because the expired air contains little of the inspired odorant.

TABLE IV

ANALYSIS OF VARIANCE FOR OLFACTORY CLEARANCE CURVES

Variance	Sum of squares	Degrees of freedom	Mean squared error	p
Between individuals	417208.825	13	32092.9865	<0.0001
Within individuals	539059.597	106	5085.46789	
Total	956268.421	119	8035.86909	

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Thus, the olfactory epithelium experiences an alternating high and low dose during each breath of the adaptation process, and this necessitates using a higher concentration of odorant to achieve adaptation at any particular level. Phenethyl alcohol was chosen as it is a pure chemical widely used in smell testing, having an odour reminiscent of roses and being reasonably well tolerated at high strength. Determination of clearance times does not suffer from this disadvantage, as the odour exposure of the olfactory epithelium is essentially zero throughout the respiratory cycle and, apart from the occasional sniff from a test bottle, the odorant should migrate from the nasal mucus exponentially, according to dilution theory. Although only a small number of subjects were included in the study, more than 100 readings were obtained; the results were thus considered to present a reliable reflection of human olfactory clearance times. Clearly, further data collection in this respect will add weight to these findings, and is the subject of ongoing research, but from our findings it can be implied that olfactory clearance occurs at a logarithmic rate.

Previous work in this field has however shown that the extent of olfactory adaptation induced is a function of both the duration and concentration of the stimulus applied.[17,18] From the clearance curves determined in our study, one notable observation is that, for physiological data, the consistent pattern of the decay times was remarkable, albeit with significant intra-subject variability from one reading to the next. In concurrence with our previous findings, the variables measured did not have any bearing on the initial olfactory thresholds achieved, and this therefore negates the need to control for these factors.[14] The absence of a significant relationship between olfactory adaptation and clearance is in contrast to the work of others in this field.[17,18] It was however noted that, just as olfactory function is noted to decline with age,[19] our findings demonstrated an age-related increase in clearance times. A 'grumpier' mood was also observed to decrease clearance times. This latter finding demonstrates that olfactory testing is affected by the subjective nature of this sensory modality. Olfactory adaptation time was also affected by nasal symptoms, whereby an increase in symptoms was related to a decrease in adaptation time.

- **This study attempted to quantify olfactory adaptation and clearance times, on presentation of a saturated solution, in a number of human volunteers, in order to determine whether these times were consistent within and between individuals**
- **Fourteen subjects performed 120 tests in total. Despite consistent linear trends within individuals, olfactory clearance times varied widely within and between individuals**
- **When testing a person's sense of smell in a clinical setting, recent exposure to similar smells should be noted, and a period of 15 minutes needs to be allowed before retesting**

Using the maximum value for olfactory clearance of phenethyl alcohol by one logarithmic threshold step would mean, for example, that a subject who achieves a threshold of 10^{-4} may potentially need a maximum of 15 minutes to allow full reversal of olfactory adaptation. The key clinical application of these results is that a period of at least 15 minutes should be left, once a subject has (potentially) adapted to phenethyl alcohol, before further olfactory testing can meaningfully be conducted on that subject, especially if they have a lower threshold. This time can be adapted, using our clearance data, according to the initial threshold achieved. This does of course make the assumption that the subject does achieve olfactory adaptation, which may not necessarily be the case; however, by making this assumption, any errors in further testing can be avoided. This may be relevant when testing with similar odours, in which case cross-reactivity is a potential issue. These issues have certainly been considered in the well established University of Pennsylvania smell identification test[20] and in the quantification of odour quality.[21]

Previous work in this field assessed olfactory adaptation and recovery times in the elderly, and found that they were more prone to adaptation and were slower to recover their threshold sensitivity.[22] Another study found that humans adapt more rapidly to malodours, such as amyl acetate, valeric acid, skatol and butyric acid, than to pleasant odours such as cis-3-hexenol and linalool.[23] This study also found that the degree of adaptation was inversely proportional to the stimulus strength, and that women responded differently to men for certain odours.

More recent work in animal models suggests that the mechanism for olfactory adaptation is a physiological one which occurs at the receptor level and is calcium-dependent.[24–26] Active pumping of calcium ions into the receptor cells results in shortening of the action potentials generated by the receptor cell axons and therefore a decreased neuronal response to the stimulus. The rise in intraciliary Ca^{2+} concentration has two opposing effects: activation of an unusual excitatory Cl^{-} conductance, and negative feedback actions on various stages of the odour transduction mechanism.[27] It has also been shown that the psychological response to prolonged olfactory stimuli can be demonstrated using olfactory event-related potentials, but this process probably represents olfactory habituation rather than adaptation.[28]

Conclusions

The main clinical implications of our olfactory testing results are that, although olfactory recovery times vary greatly both within and between individuals, sufficient rest intervals should be allowed between testing of similar odours – a minimum duration of 15 minutes is recommended in the case of phenethyl alcohol.

References

1 Wysocki CJ, Gilbert AN. National Geographic smell survey. effects of age are heterogenous. *Ann N Y Acad Sci* 1989;**561**:12–28
2 Olsson MJ, Cain WS. Psychometrics of odor quality discrimination: method for threshold determination. *Chem Senses* 2000;**25**:493–9
3 Carrie S, Scannell JW, Dawes PJ. The smell map: is there a commonality of odour perception? *Clin Otolaryngol Allied Sci* 1999;**24**:184–9
4 Dawes PJ, Dawes MT, Williams SM. The smell map: commonality of odour perception confirmed. *Clin Otolaryngol* 2004;**29**:648–54
5 Dalton P. Psychophysical and behavioral characteristics of olfactory adaptation. *Chem Senses* 2000;**25**:487–92
6 Zufall F, Leinders-Zufall T. The cellular and molecular basis of odor adaptation. *Chem Senses* 2000;**25**:473–81
7 Best AR, Wilson DA. Coordinate synaptic mechanisms contributing to olfactory cortical adaptation. *J Neurosci* 2004;**24**:652–60
8 Zufall F, Shepherd GM, Firestein S. Inhibition of the olfactory cyclic nucleotide gated ion channel by intracellular calcium. *Proceedings Biological Sciences/The Royal Society of London* 1991;**246**:225–30
9 Potter H, Chorover SL. Response plasticity in hamster olfactory bulb: peripheral and central processes. *Brain Res* 1976;**116**:417–29
10 Mair RG, Gesteland RC, Blank DL. Changes in morphology and physiology of olfactory receptor cilia during development. *Neuroscience* 1982;**7**:3091–103
11 McCollum J, Larson J, Otto T, Schottler F, Granger R, Lynch G. Short-latency single-unit processing in olfactory cortex. *J Cogn Neurosci* 1991;**3**:293–9
12 Wilson DA. Habituation of odor responses in the rat anterior piriform cortex. *J Neurophysiol* 1998;**79**:1425–40
13 Aronsohn E. Experimental investigations into the physiology of smell [in German]. *Archiv Physiolol Leipzig* 1886;**57**:321–57
14 Philpott C, Goodenough P, Robertson A, Passant C, Murty G. The effect of temperature, humidity and peak inspiratory nasal flow on olfactory thresholds. *Clin Otolaryngol Allied Sci* 2004;**29**:24–31
15 Philpott C, Goodenough P, Wolstenholme C, Murty G. What solvent for olfactory testing? *Clin Otolaryngol Allied Sci* 2004;**29**:667–71
16 Doty R, Gregor T, Settle R. Influence of intertrial interval and sniff bottle volume on phenyl ethyl alcohol odor detection thresholds. *Chem Senses* 1986;**11**:259–64
17 Doty RL, Laing D. Psychophysical measurement of human olfactory function. In: Doty RL, ed. *Handbook of Olfaction and Gustation*, 2nd edn. New York: Marcel Dekker, 2003;203–228
18 Koster E, de Wijk R. Olfactory adaptation. In: Laing D, Doty R, Breipohl W, eds. *The Human Sense of Smell*. Berlin: Springer-Verlag, 1991;199–215
19 Murphy C, Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM. Prevalence of olfactory impairment in older adults. *JAMA* 2002;**288**:2307–12
20 Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. *Physiol Behav* 1984;**32**:489–502
21 Wise PM, Olsson MJ, Cain WS. Quantification of odor quality. *Chem Senses* 2000;**25**:429–43
22 Stevens JC, Cain WS, Schiet FT, Oatley MW. Olfactory adaptation and recovery in old age. *Perception* 1989;**18**:265–76
23 Jacob TJ, Fraser C, Wang L, Walker V, O'Connor S. Psychophysical evaluation of responses to pleasant and mal-odour stimulation in human subjects; adaptation, dose response and gender differences. *Int J Psychophysiol* 2003;**48**:67–80
24 Reidl J, Borowski P, Sensse A, Starke J, Zapotocky M, Eiswirth M. Model of calcium oscillations due to negative feedback in olfactory cilia. *Biophys J* 2006;**90**:1147–55
25 Reisert J, Matthews HR. Adaptation of the odour-induced response in frog olfactory receptor cells. *J Physiol (Lond)* 1999;**3**:801–13
26 Yee KK, Wysocki CJ. Odorant exposure increases olfactory sensitivity: olfactory epithelium is implicated. *Physiol Behav* 2001;**72**:705–11
27 Matthews HR, Reisert J. Calcium, the two-faced messenger of olfactory transduction and adaptation. *Curr Opin Neurobiol* 2003;**13**:469–75
28 Wang L, Walker VE, Sardi H, Fraser C, Jacob TJ. The correlation between physiological and psychological responses to odour stimulation in human subjects. *Clinical Neurophysiology* 2002;**113**:542–51

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