Published in final edited form as:

Psychol Aging. 2011 December ; 26(4): 864–871. doi:10.1037/a0023263.

Genetic and Environmental Influences on Odor Identification Ability in the Very Old

Richard L. Doty,

Smell & Taste Center, University of Pennsylvania

Inge Petersen,

Institute of Public Health, University of Southern Denmark, Odense, Denmark, and Department of Clinical Biochemistry and Department of Clinical Genetics, Odense University Hospital, Odense, Denmark

Nii Mensah, and

Smell & Taste Center, University of Pennsylvania

Kaare Christensen

Institute of Public Health, University of Southern Denmark, Odense, Denmark, and Department of Clinical Biochemistry and Department of Clinical Genetics, Odense University Hospital, Odense, Denmark

Abstract

Odor identification ability and cognition were measured in a population-based cohort of 1,222 very old twins and singletons, including 91 centenarians. Heritability for identifying odors was low, in contrast to that for cognition. Common genes were found to contribute to both olfaction and cognition. In a multiple regression model, sex, age, cognitive function, and smoking, but not APOEε4 status, were significant predictors of the olfactory test scores (all p s < 0.001). This study, along with data from other studies, suggests that indices of heritability for odor identification decline with age, likely reflecting adverse environmental influences on the smell system.

Keywords

olfaction; genetics; epidemiology; cognition; age

The ability to smell decreases with age (Doty, 1989; Hoffman, Ishii, & Macturk, 1998; Murphy et al., 2002; Schiffman, 1991). In a study of nearly 2,000 subjects, three-quarters of those over 80 years of age exhibited smell loss on a standardized odor identification test, and over half of those between the ages of 65 and 80 years did so (Doty, Shaman, & Dann, 1984). Such decrements pose a serious health risk and greatly impair quality of life. Thus, a disproportionate number of elderly die in accidental gas poisonings (Chalke, Dewhurst, & Ward, 1958) and a number suffer, as a result of their olfactory loss, from anorexia and nutritional deficits (Duffy, Backstrand, & Ferris, 1995; Drewnowski & Shultz, 2001).

© 2011 American Psychological Association

Correspondence concerning this article should be addressed to Richard L. Doty, Smell and Taste Center, Hospital of the University of Pennsylvania, 5 Ravdin Pavilion, 3400 Spruce Street, Philadelphia, PA 19104. doty@mail.med.upenn.edu.

Conflict of Interest: RLD is President and major shareholder of Sensonics, Inc., the manufacturer and distributor of the olfactory tests employed in this study. No other conflicts of interest are noted.

Smell loss, particularly in conjunction with risk factors for cognitive decline (e.g., APOE ϵ 4), is associated with Alzheimer's disease (AD) and some other age-related disorders (Graves et al., 1999; Doty, 2003). While AD-related pathology may contribute to the smell loss of some elderly, other factors are likely prepotent. Among such factors are cumulative damage to the olfactory epithelium from viruses and other xenobiotics (Loo, Youngentob, Kent, & Schwob, 1996) and occlusion of cribriform plate foramina through which the olfactory nerve axons pass from the nasal cavity to the brain (Kalmey, Thewissen, & Dluzen, 1998).

Aside from studies reporting an association between the APOE ϵ 4 isoform and age-related olfactory decline (e.g., Olofsson et al., 2010), little attention has been paid to the role of genetics, alone or in combination with other factors, in influencing olfactory function of older persons. Most studies that have addressed this problem in nonelderly cohorts have noted relatively low heritability for measures of odor identification and detection. For example, Hubert, Fabsitz, Feinleib, & Brown (1980) tested detection thresholds for acetic acid, isobutyric acid, and cyclohexanone in 51 male monozygotic (MZ) and 46 male dizygotic (DZ) twin pairs 42 to 56 years of age and found no evidence of inheritance. Segal, Topolski, Wilson, Brown, & Araki (1995) administered the 40-odorant University of Pennsylvania Smell Identification Test (Doty et al., 1984) to 45 MZ, mean (*SD*) age = 29.38 (18.14), and 37 DZ twin pairs, mean (*SD*) age = 21.90 (9.59). While the MZ intraclass correlation was 0.31 and the DZ intraclass correlation was 0.15, these values did not differ significantly. More recently, Finkel, Pedersen, & Larsson (2001) administered tests of odor identification, intensity, and pleasantness to 86 monozygotic twin pairs and 141 dizygotic twin pairs with a mean (*SD*) age of 67 (7.1) years. They concluded that only modest heritability existed for their olfactory function measures, with genetic contributions ranging from 14% for odor detection to 29% for odor identification.

In the first genome-wide human study on this topic, Knaapila et al. (2007) administered the 12-item Brief Smell Identification Test (B-SIT) (Doty, Marcus, & Lee, 1996) to 146 adults, mean (*SD*) age = 49.1 (14.8) years, from 26 families. The goal was to identify loci affecting the identification, intensity, and hedonics of the 12 stimuli. Genetic linkage for identification of the five odorants that exhibited the most performance variation was not found, although ratings of the intensity of paint thinner and the pleasantness of cinnamon were linked to separate loci that reportedly harbor no odorant receptor genes (i.e., 4 and 2p). In a subsequent study, this group performed quantitative genetic modeling of intensity and pleasantness ratings given to six odorants (cinnamon, chocolate, turpentine, isovaleric acid, vanilla, androstenone, lemon) by 856 twins, which included 83 complete monozygotic and 275 dizygotic twin pairs, mean (*SD*) age = 29.5 (14.1) years (Knaapila et al., 2008b). They reported (p. 490) that "nonshared (individual, specific) environmental effects are the most prominent factors underlying the phenotypic variation in these traits. In contrast, strong genetic effects were not detected." These general findings were supported in a subsequent study in which their sample size was expanded to 1,311 twins, mean (*SD*) age = 28.6 (16.5) years (Knaapila et al., 2008a).

In contrast to the aforementioned findings are studies reporting significant influences of heredity on measures of odor identification and detection, mainly in young cohorts. Gross-Isseroff, Ophir, Bartana, Voet, & Lancet (1992) studied 17 MZ and 15 DZ twin pairs, mean (*SEM*) age = 12.5 (0.29), and reported a strong genetic component for androstenone and isoamyl acetate, but not for citral or eugenol (respective MZ intraclass correlations = 0.78, 0.73, 0.35 & -0.05; respective DZ intraclass correlations = 0.00, 0.00, 0.16 & 0.43). Other positive results come from an experiment by Wysocki & Beauchamp (1984). Androstenone and pyridine detection thresholds were determined for 17 MZ and 21 DZ twin pairs ranging in age from 17 to 21 years. All of the MZ twin pairs were in agreement for sensitivity/

insensitivity to androstenone, whereas only 61% of the DZ twin pairs were in such agreement. No genetic influence on pyridine sensitivity was found. More recently, Keller, Zhuang, Chi, Vossahl, & Matsunami (2007) reported that persons with a receptor variant that significantly impairs, in vitro, the function of a receptor activated by the odorants androstenone and androstadienone were less sensitive to these odorants. The age of the participants was not indicated.

The present study assessed odor identification ability and cognition in a population-based cohort of very old twins and singletons. All subjects were 70 or more years of age and many were over 100. Our primary goal was to determine the relative contribution of common genes on these two traits and the relationship between them in this unique population. This was of specific interest in light of varied reports of heritability in younger cohorts and evidence that smell loss is among the first signs of Alzheimer's disease (Hawkes & Doty, 2009). A secondary goal was to establish the influences of such variables as age, sex, smoking behavior, and health on smell function and to control such factors in our genetic analyses.

Subjects and Methods

Study Population

The sample was comprised of participants from two Danish nationwide population-based surveys, the Longitudinal Study of Aging Danish Twins (LSADT) and the Danish 1905-Cohort 2005 survey. Those eligible from LSADT 2005 were Danish twins aged 70 + years in 2001 and still living in Denmark. The eligible participants from the Danish 1905-Cohort 2005 survey were all Danes born in 1905 and still living in Denmark. Details of both surveys have been previously described (Christensen, Holm, McGue, Corder, & Vaupel, 1999; Christensen et al., 2000b; Christensen, Holm, & Vaupel, 1996; Christensen, Gaist, Jeune, & Vaupel, 1998; Christensen et al., 2000a; McGue & Christensen, 1997; McGue & Christensen, 2001; Nybo et al., 2001a; Nybo et al., 2001b; Nybo et al., 2003). The subjects who provided complete responses to all of the odor test items (see next section) included 91 centenarians, 18 men and 73 women; respective mean (*SD*) ages = 99.83 (0.28) & 99.63 (0.29), and 1,131 elderly twins under the age of 100 years, 513 men and 618 women, respective mean (*SD*) ages = 79.65 (4.53) & 81.17 (5.17).

Olfactory Test

A modified version of the 12-odorant B-SIT was administered (Doty et al., 1996). Each stimulus was accompanied by four odor-related response categories and one "don't know" category. Since only 10.5% and 29.5% of the subjects, respectively, could identify the turpentine and lemon odors, these items were excluded from analysis.

Zygosity

The zygosity of the participating twins was determined using a brief questionnaire on physical similarity. This questionnaire has been previously validated and shown to be very reliable, with misclassification being less than 5% (Christiansen et al., 2003).

Cognitive Test Measures

In addition to the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975), measures of fluency (number of animals named in one minute), forward and backward digit short-term memory, and immediate and delayed recall of a list of 12 nouns were obtained from 1,229 twins (93%) and 146 centenarians (77%). As in earlier work (e.g., McGue & Christensen, 2001), a cognitive composite score was formed from the sum of the standard scores of these latter five tests, increasing test reliability. These tests had been shown to be

correlated with one another; e.g., fluency, memory $r = .46$; animals, digit span $r = .33$; memory, digit span $r = .34$.

Other Measures

The following survey information was employed in this study: social group status, as defined by the Danish National Center for Social Research (Hansen, 1984), and indices of self-rated health (5 levels), activity of daily living (Nybo et al., 2001b), psychological depression (McGue & Christensen, 1997), hearing loss (Christensen, Frederiksen and Hoffman, 2001), and smoking behavior. APOE genotypes were obtained for 400 twins and 137 centenarians.

Data Analysis

The number of correct B-SIT item responses was calculated (total possible = 10). “Don’t know” was classified as a wrong answer. Univariate association studies were carried out for all covariates under consideration, i.e., sex, age, APOE genotype, zygosity, social grouping, self-rated health, ADL, depression score, MMSE, cognitive composite, hearing ability, and smoking status. The association analyses were repeated with age stratified into three groups: 74–79, 80–84, and 80 + years. Multiple linear regression was performed between the number of correctly identified odors and quartiles of cognitive abilities adjusted for the aforementioned covariates.

Analyses of Twin Similarity

The similarity between monozygotic (MZ) and dizygotic (DZ) twins was assessed using intraclass correlations for the traits. This classic twin study methodology assumes that MZ twins have identical genotypes, whereas DZ twins share, on average, 50% of their genes and are no more genetically related than ordinary siblings. A greater phenotypic similarity in MZ than in DZ twins is expected when a significant genetic component to the trait variation is present.

Estimation of Heritability

According to standard biometric practice (e.g., Neale & Cardon, 1992), assuming no genetic inter-locus interaction (epistasis), no gene-environment interaction, and no assortative mating, the phenotypic variance of individuals can be separated into variance due to additive genetic effects (V_a or A), genetic dominance (V_d or D), shared environment (V_c or C), and nonshared environment (V_e or E), i.e., $V_{\text{total}} = V_a + V_d + V_c + V_e$. Only nonshared environment contributes to dissimilarity within MZ twin pairs because of their genetic identity, whereas the effects of additive genetic factors and genetic dominance may also contribute to dissimilarity within DZ pairs, who share, on average, one-half of the additive genetic factors and one-quarter of the dominant genetic factors. Hence, for MZ pairs, the covariance is given by $\text{Cov}(\text{twin 1, twin 2}) = V_a + V_d + V_c$, whereas for DZ pairs it takes the form $\text{Cov}(\text{twin 1, twin 2}) = [1/2]V_a + [1/4]V_d + V_c$. In standard biometric models, the shared environmental component (V_c) and the dominant genetic variance component (V_d) cannot be estimated simultaneously. We therefore fitted ACE and ADE models, along with simpler models (AE-, CE-, and E-models), to the data. Each model was evaluated in terms of whether it fitted the data (i.e. had a nonsignificant Chi square goodness-of-fit test statistic) and was parsimonious (i.e. none of the parameters could be deleted without a significant increase in the Chi square test statistic). For a comparison of non-nested models, the Akaike Information Criterion ($\text{AIC} = -2 \text{ LL} - 2 \text{ df}$) was used. Models with the lowest AIC were preferred.

Extension of the univariate models to a bivariate model, including both odor identification and the cognitive composite, additionally allowed for assessing whether and to what extent the correlation between the two traits can be explained by common genes, i.e. genetic correlation (r_g), or shared environment, i.e., the environmental correlation (r_e).

Confounder Control

The twin similarity and heritability analyses were adjusted for age and sex by including these in the mean variance. Separate models also adjusting for smoking status were implemented for twin similarity and for univariate and bivariate heritability estimation.

Software

Stata 9 was used for association and regression analyses, while the Mx statistical program (<http://www.vcu.edu/mx>) was used for structural equation modeling (Neale, Boker, Xie & Maes, 2003).

Results

The mean B-SIT scores are shown for the men and women as a function of age in Figure 1. It is apparent that the test scores were consistently higher in women than in men and monotonically decreased as a function of age.

Univariate Association Analyses

In the univariate analyses, women were better at identifying odors than men (respective means [SD] = 6.4 [2.4] and 6.1 [2.4], $p < .02$), despite being older (83.1 [5.3] vs. 80.3 [4.6] years). Age, characterized into 74–79, 80–84 and 85+ year groups, was associated with odor identification ability (respective means [SD] = 7.0 [2.1], 6.2 [2.4] and 4.9 [2.6], $p < .001$), as was social group (respective means [SD] for groups I–V = 6.7 [2.6], 6.6 [2.2], 6.0 [2.4], 6.3 [2.4] and 5.9 [2.4], $p < .001$), self-rated health (means [SD] for excellent = 6.7 [2.2], good = 6.3 [2.5], acceptable = 6.1 [2.5], and poor or very poor = 5.5 [2.6], $p < .01$), ADL-strength scores (quartile means [SD] = 6.8 [2.2], 6.5 [2.3], 6.0 [2.4] and 5.1 [2.6], $p < .001$), depression symptom scores (quartile means [SD] = 6.6 [2.3], 6.3 [2.4], 6.4 [2.3] and 5.6 [2.6], $p < .001$), MMSE scores (quartile means [SD] = 4.4 [2.8], 6.1 [2.4], 6.5 [2.4] and 7.0 [2.2], $p < .001$); cognitive composite scores (quartile means [SD] = 4.9 [2.5], 6.2 [2.3], 6.8 [2.2] and 7.2 [2.2], $p < .001$); and hearing ability (dichotomized means [SD] for without difficulty = 6.6 [2.3] and three other groups = 5.9 [2.5], $p < .001$). Although past smokers scored higher on the odor identification test than current smokers and never smokers (respective means [SD] = 6.5 [2.4], 6.0 [2.4], and 6.1 [2.5], $p < .02$), stratification by age group showed this result was confounded by age. Overall, the aforementioned findings indicate that better physical and mental health and higher social position were associated with better ability to identify odors.

Multiple Association Analyses

The results of the multiple linear regression analyses are shown in Table 1. When all variables were included in the regression model, the only significant associations were sex, age, cognitive functioning, and smoking (all p s < 0.001). Forward and backward stepwise estimation regression (using $p = .20$ as the criterion for inclusion/exclusion) showed the same results. On average, those participants in the highest quartile of the cognitive test battery were able to correctly identify 1.83 more test items than those in the lowest quartile (2.23 for men and 1.5 for women). Women identified 0.66 more odor items than men. On average, a 74-year-old person identified 3.38 more items than a 100-year-old person (3.33 for men and 3.49 for women).

Heritability

Table 2 shows the results of the univariate twin analyses. The difference in intraclass correlation for the odor identification test score between MZ and DZ twins was statistically insignificant ($p = .25$), and both correlations were not statistically significant from zero. However, the intraclass correlations for cognition were significant and more than twice as large for MZ than DZ twins ($p < .001$), implying a relatively strong genetic influence on the variance of the cognitive composite test measure.

Employment of the E-model found no significant heritability for odor identification (Table 2). For cognition, the AE-model provided the best fit to the data: the sex- and age-adjusted heritability was 0.70 (95% CI: 0.59–0.77). The bivariate model, which had higher statistical power, found both the odor identification and the cognitive composite scores to have statistically significant genetic component, despite the fact that the heritability of odor identification performance was low, 0.13 (0.01; 0.31); Table 3. The genetic correlation between the two traits was substantial and significantly different from 0 ($r_g = 0.64$ [0.19; 1.00]), suggesting that common genes contribute to the regulation of the two traits (i.e. pleiotropy).

Discussion

The present findings suggest that odor identification ability is influenced by age, sex, and cigarette smoking even in the oldest of the elderly, as occurs in younger cohorts (Doty et al., 1984; Doty & Cameron, 2009; Frye, Schwartz, & Doty, 1990; Murphy, 1985). Moreover, these findings indicate that such ability, while associated with very low heritability estimates, is associated with cognitive function. Thus, both odor identification and cognition had statistically significant genetic components in the bivariate model even though the intraclass correlations of the MZ and DZ twins for the olfactory test scores did not differ significantly from one another and heritability for odor identification was low and non-significant in the univariate model. While it may appear paradoxical that a strong genetic correlation and olfaction can be present in light of low heritability estimates for olfactory function, such a paradox is easy to explain on the basis of covariance. Thus, the genetic correlation is defined as the off-diagonal element of the standardized additive genetic covariance matrix. A positive genetic correlation suggests that the two traits are influenced by common genes and can be high regardless of the low heritability of the two traits under consideration (Neale & Cardon, 1999).

Our results are in general accord with earlier reports that most of the variation observed in odor identification performance, save that due to gender, is due to noninherited factors (Hubert et al., 1980; Knaapila et al., 2007; Knaapila et al., 2008a; Knaapila et al., 2008b; Segal et al., 1995). Among the most salient of such factors are viral, bacterial, and other xenobiotic insults that cumulatively damage the olfactory epithelium (Calderon-Garciduenas et al., 2010; Doty, 2008; Jafek et al., 1990; Nakashima, Kimmelman, & Snow, Jr., 1984; Naessen, 1971). Other factors to be considered include age-related ossification of the foramina of the cribriform plate (Kalmey et al., 1998) and the development of age-related brain pathology, including Lewy bodies, neurofibrillary tangles, and β -amyloid and α -synuclein deposits within the olfactory bulbs, tracts, amygdala, piriform cortex, and entorhinal cortex (for review, see Smutzer et al., 2003). Transgenic mice that overexpress tau, which is associated with the development of neurofibrillary tangles and threads, exhibit olfactory dysfunction (Macknin, Higuchi, Lee, Trojanowski, & Doty, 2004), whereas transgenic mice that overexpress β -amyloid, the major aberrant protein associated with neuritic plaques, do not (Zhuo et al., 2007).

Given the fact that the number of environmental insults to the olfactory system increases as a function of age, one might expect heritability coefficients to decline with advancing age, since any variability due to genetics is likely swamped by variability from environmental and perhaps other factors. The limited data suggest this to be the case. Thus, the heritability coefficients observed in this study, although positive, were low (0.13 and 0.16). These values fall below those noted for odor identification by Finkel et al. (2001) – 0.25 in a study group whose average age was 67.1 years and by Segal et al. (1995) – 0.31 in a study group whose average age was 26 years of age. Moreover, those studies that have observed the largest heritability coefficients are those that have examined the youngest persons. Thus, Gross-Isseroff et al. (1992) noted monozygotic intraclass correlations as high as 0.78 in twins whose average age was 12.5 years. The age of monozygotic twins found by Wysocki & Beauchamp (1984) to be in agreement for sensitivity/insensitivity to androsthenone was 21 years. Contrary to the pattern of age-related heritability seen for olfaction, however, the genetic influence on cognitive functioning does not attenuate with age (McClearn et al., 1997; McGue & Christensen, 2001; McGue, Osler, & Christensen, 2010).

Another factor that may contribute to the size of heritability coefficients is the chemical nature of the stimulus. In this study, as well as in most other studies examining odor identification, the olfactory stimuli are made up of multiple, not single, chemicals. Multiple chemicals, which in nature are more common signifiers of discernable odors, activate a range of receptors in varying numbers to mediate a particular odor quality. However, when any one of the underlying receptors is missing, e.g., as a result of genetics, the remaining receptors most likely provide enough information to mimic to a large degree the sensation that would be present if all receptor types were functioning. Thus, the brain ‘fills in’ information that is lacking to provide an overall percept, much as occurs in vision when elements of the visual field are absent (Wilson & Stevenson, 2006). Therefore, an odor percept based upon unitary chemicals that stimulate more limited numbers of receptors would be more apt to be affected by genetic variation associated with those few receptors. With rare exception (e.g., Hubert et al., 1980), the existing literature is in accord with this concept. Thus, those studies that have reported the largest heritability have typically employed single chemicals (e.g., Finkel et al., 2001; Gross-Isseroff et al., 1992; Wysocki & Beauchamp, 1984).

Our finding of a genetic association between odor identification and cognition has precedence. For example, Finkel et al. (2001) reported, also using a bivariate analysis, a correlation between odor identification test scores and cognitive measures in MZ, but not DZ, twins. Other studies have noted, in nontwin populations, correlations between odor identification test scores and measures of cognitive function, most notably ones associated with verbal processing (Larsson, Finkel, & Pedersen, 2000). Indeed, several authors have made the argument that olfactory and language share cortical resources (e.g., Lorig, 1999; Larsson, Lovden, & Nilsson, 2003). Support for his argument comes, in part, from evidence that verbal tasks are adversely altered more by olfactory than auditory or visual stimuli (Lorig, Elmes, & Yoerg, 1998). The sex difference noted in the present study may reflect, at least in part, greater utilization of semantic strategies by women for both encoding and recalling odor memories (Larsson et al., 2003). Such strategies enhance, in general, performance on odor identification and memory tests (Choudhury, Moberg, & Doty, 2003; Lehrner, 1993; Lyman & McDaniel, 1990; Rabin & Cain, 1984; Walk & Johns, 1984).

Although the present results imply that common genes are associated with both olfactory and cognitive function in the oldest of the elderly—an association that has been suggested by others in younger cohorts—the specific nature of this relationship is unclear. It is noteworthy that associations between cognitive function and other sensory measures, namely auditory thresholds and refraction-corrected visual acuity, have been reported in older cohorts (Baltes

and Lindenberger, 1997; Lindenberger & Baltes, 1994), a phenomenon that may reflect general age-related changes in brain function (Baltes & Lindenberger, 1997). If the association between cognitive and olfactory function observed in this study is dependent upon central neural processes, then the implication would be that common genes contribute to these processes. However, the nature of this dependency is also not clear. Is a common set of genes protecting or placing at risk brain regions associated with age-related olfactory and cognitive pathology? Are common neurotransmitters or neuromodulators involved? Are the concordances primarily due to abilities to encode, retain, or recall information, rather than to general relationships between olfaction and cognition, per se? Whatever the involved associations, it is likely that they are component of a multifactorial interplay between genes and the environment that is in sore need of thorough study.

Acknowledgments

We thank Isabelle Tourbier for her aid in the initial stages of this project. This work was supported, in part, by NIA RO1 AG17496 and USAMRAA W81XWH-09-1-0467 awarded to RLD. The Longitudinal Study of Aging Danish Twins (LSADT) is supported, in part, by NIA P01 AG008761. The Danish Aging Research Center is supported, in part, by a grant from the VELUX foundation. The Longitudinal Study of Aging Danish Twins (LSADT) has been approved by the Regional Danish Scientific-Ethical Committee (ID# VF 20040241) and the Danish Data Protection Agency (J.nr. # 2000-54-0047). The Longitudinal Study of the 1905 Birth Cohort (1905-Cohort) was approved by the Regional Danish Scientific-Ethical Committee (ID# VF 20040240) and the Danish Data Protection Agency (J.nr. # 2004-41-4651). No funders had any role in the study design, analysis, or writing of this paper.

References

- Baltes PB, Lindenberger U. Emergence of a powerful connection between sensory and cognitive functions across the adult life span: A new window to the study of cognitive aging? *Psychology and Aging*. 1997; 12:12–21. [PubMed: 9100264]
- Calderon-Garciduenas L, Franco-Lira M, Henriquez-Roldan C, Osnaya N, Gonzalez-Maciel A, Reynoso-Robles R, Doty RL. Urban air pollution: Influences on olfactory function and pathology in exposed children and young adults. *Experimental and Toxicological Pathology*. 2010; 62:91–102.
- Chalke HD, Dewhurst JR, Ward CW. Loss of smell in old people. *Public Health (London)*. 1958; 72:223–230.
- Choudhury ES, Moberg P, Doty RL. Influences of age and sex on a microencapsulated odor memory test. *Chemical Senses*. 2003; 28:799–805. [PubMed: 14654448]
- Christensen K, Gaist D, Jeune B, Vaupel JW. A tooth per child? *Lancet*. 1998; 352:204. [PubMed: 9683217]
- Christensen K, Holm NV, McGue M, Corder L, Vaupel JW. A Danish population-based twin study on general health in the elderly. *Journal of Aging and Health*. 1999; 11:49–64. [PubMed: 10848141]
- Christensen K, Holm NV, Vaupel JW. Alzheimer's disease in twins. *Lancet*. 1996; 347:976. [PubMed: 8598793]
- Christensen K, Kristiansen M, Hagen-Larsen H, Skytthe A, Bathum L, Jeune B, Ørstavik KH. X-linked genetic factors regulate hematopoietic stem-cell kinetics in females. *Blood*. 2000a; 95:2449–2451. [PubMed: 10733522]
- Christensen K, McGue M, Yashin A, Iachine I, Holm NV, Vaupel JW. Genetic and environmental influences on functional abilities in Danish twins aged 75 years and older. *Journals of Gerontology Series A-Biological Sciences & Medical Sciences*. 2000b; 55:M446–M452.
- Christensen K, Frederiksen H, Hoffman HJ. . *Journal of the American Geriatrics Society*. 2001; 49:1512–1517. [PubMed: 11890591]
- Christiansen L, Frederiksen H, Schousboe K, Skytthe A, von Wurmb-Schwark N, Christensen K, Kyvik K. Age- and sex-differences in the validity of questionnaire-based zygosity in twins. *Twin Research*. 2003; 6:275–278. [PubMed: 14511432]
- Doty RL. Influence of age and age-related diseases on olfactory function. *Annals of the New York Academy of Sciences*. 1989; 561:76–86. [PubMed: 2525363]

- Doty, RL. Odor perception in neurodegenerative diseases. In: Doty, RL., editor. Handbook of Olfaction and Gustation. 2nd ed.. New York: Marcel Dekker; 2003. p. 479-502.
- Doty RL. The olfactory vector hypothesis of neurodegenerative disease: Is it viable? *Annals of Neurology*. 2008; 63:7–15. [PubMed: 18232016]
- Doty RL, Cameron EL. Sex differences and reproductive hormone influences on human odor perception. *Physiology & Behavior*. 2009; 97:213–228. [PubMed: 19272398]
- Doty RL, Marcus A, Lee WW. Development of the 12-item cross-cultural smell identification test (CC-SIT). *Laryngoscope*. 1996; 106:353–356. [PubMed: 8614203]
- Doty RL, Shaman P, Applebaum SL, Giberson R, Siksorski L, Rosenberg L. Smell identification ability: Changes with age. *Science*. 1984; 226:1441–1443. [PubMed: 6505700]
- Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: A standardized microencapsulated test of olfactory function. *Physiology & Behavior*. 1984; 32:489–502. [PubMed: 6463130]
- Drewnowski A, Shultz JM. Impact of aging on eating behaviors, food choices, nutrition, and health status. *Journal of Nutrition, Health & Aging*. 2001; 5:75–79.
- Duffy VB, Backstrand JR, Ferris AM. Olfactory dysfunction and related nutritional risk in free-living, elderly women. *Journal of the American Dietetic Association*. 1995; 8:879–884. [PubMed: 7636078]
- Finkel D, Pedersen NL, Larsson M. Olfactory functioning and cognitive abilities: A twin study. *Journals of Gerontology Series B-Psychological Sciences & Social Sciences*. 2001; 56:226–233.
- Folstein MF, Folstein SE, McHugh PR. “Mini-Mental State”: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*. 1975; 12:189–198. [PubMed: 1202204]
- Frye RE, Schwartz BS, Doty RL. Dose-related effects of cigarette smoking on olfactory function. *Journal of the American Medical Association*. 1990; 263:1233–1236. [PubMed: 2304239]
- Graves AB, Bowen JD, Rajaram L, McCormick WC, McCurry SM, Schellenberg GD, Larson EB. Impaired olfaction as a marker for cognitive decline: Interaction with apolipoprotein E epsilon4 status. *Neurology*. 1999; 53:1480–1487. [PubMed: 10534255]
- Gross-Isseroff R, Ophir D, Bartana A, Voet H, Lancet D. Evidence for genetic determination in human twins of olfactory thresholds for a standard odorant. *Neuroscience Letters*. 1992; 141:115–118. [PubMed: 1508392]
- Hansen, EJ. Socialgrupper i Danmark. SFI Studie 48. Copenhagen: Socialforskningsinstituttet; 1984. [Social groups in Denmark, SFI Study 48].
- Hawkes, CH.; Doty, RL. *The Neurology of Olfaction*. Cambridge, MA: Cambridge University Press; 2009.
- Hoffman HJ, Ishii EK, Macturk RH. Age-related changes in the prevalence of smell/taste problems among the United States adult population. Results of the 1994 disability supplement to the National Health Interview Survey (NHIS). *Annals of the New York Academy of Sciences*. 1998; 855:716–722. [PubMed: 9929676]
- Hubert HB, Fabsitz RR, Feinleib M, Brown KS. Olfactory sensitivity in humans: Genetic versus environmental control. *Science*. 1980; 208:607–609. [PubMed: 7189296]
- Jafek BW, Hartman D, Eller PM, Johnson EW, Strahan RC, Moran DT. Postviral olfactory dysfunction. *American Journal of Rhinology*. 1990; 4:91–100.
- Kalmey JK, Thewissen JG, Dluzen DE. Age-related size reduction of foramina in the cribriform plate. *Anatomical Record*. 1998; 251:326–329. [PubMed: 9669759]
- Keller A, Zhuang H, Chi Q, Vosshall LB, Matsunami H. Genetic variation in a human odorant receptor alters odour perception. *Nature*. 2007; 449:468–472. [PubMed: 17873857]
- Knaapila A, Keskitalo K, Kallela M, Wessman M, Sammalisto S, Hiekkalinna T, Perola M. Genetic component of identification, intensity and pleasantness of odours: A Finnish family study. *European Journal of Human Genetics*. 2007; 15:596–602. [PubMed: 17342154]
- Knaapila A, Tuorila H, Kyvik KO, Wright MJ, Keskitalo K, Hansen J, Silventoinen K. Self-ratings of olfactory function reflect odor annoyance rather than olfactory acuity. *Laryngoscope*. 2008a; 118:2212–2217. [PubMed: 18948833]

- Knaapila A, Tuorila H, Silventoinen K, Wright MJ, Kyvik KO, Keskitalo K, Perola M. Environmental effects exceed genetic effects on perceived intensity and pleasantness of several odors: A three-population twin study. *Behavior Genetics*. 2008b; 38:484–492. [PubMed: 18543092]
- Larsson M, Finkel D, Pedersen NL. Odor identification: Influences of age, gender, cognition, and personality. *Journals of Gerontology Series B-Psychological Sciences & Social Sciences*. 2000; 55:304–310.
- Larsson M, Lovden M, Nilsson LG. Sex differences in recollective experience for olfactory and verbal information. *Acta Psychologica*. 2003; 112:89–103. [PubMed: 12423901]
- Lehrner JP. Gender differences in long-term odor recognition memory: Verbal versus sensory influences and the consistency of label use. *Chemical Senses*. 1993; 18:17–26.
- Lindenberger U, Baltes PB. Sensory functioning and intelligence in old age: A strong connection. *Psychology and Aging*. 1994; 9:339–355. [PubMed: 7999320]
- Loo AT, Youngentob SL, Kent PF, Schwob JE. The aging olfactory epithelium: Neurogenesis, response to damage, and odorant-induced activity. *International Journal of Developmental Neuroscience*. 1996; 14:881–900. [PubMed: 9010732]
- Lorig TS. On the similarity of odor and language perception. *Neuroscience & Biobehavioral Reviews*. 1999; 23:391–398. [PubMed: 9989426]
- Lorig TS, Elmes DG, Yoerg VL. Chemosensory alteration of information processing. *Annals of the New York Academy of Sciences*. 1998; 855:591–597. [PubMed: 9929655]
- Lyman BJ, McDaniel MA. Memory for odors and odor names: Modalities of elaboration and imagery. *Journal of Experimental Psychology: Learning, Memory, & Cognition*. 1990; 16:656–664.
- Macknin JB, Higuchi M, Lee VM, Trojanowski JQ, Doty RL. Olfactory dysfunction occurs in transgenic mice overexpressing human tau protein. *Brain Research*. 2004; 1000:174–178. [PubMed: 15053964]
- McClearn GE, Johansson B, Berg S, Pedersen NL, Ahern F, Petrill SA, Plomin R. Substantial genetic influence on cognitive abilities in twins 80 or more years old. *Science*. 1997; 276:1560–1563. [PubMed: 9171059]
- McGue M, Christensen K. Genetic and environmental contributions to depression symptomatology: Evidence from Danish twins 75 years of age and older. *Journal of Abnormal Psychology*. 1997; 106:439–448. [PubMed: 9241945]
- McGue M, Christensen K. The heritability of cognitive functioning in very old adults: Evidence from Danish twins aged 75 years and older. *Psychology and Aging*. 2001; 16:272–280. [PubMed: 11405315]
- McGue M, Osler M, Christensen K. Causal inference and observational research: The utility of twins. *Perspectives on Psychological Science*. 2010; 5:546–556. [PubMed: 21593989]
- Murphy C. Cognitive and chemosensory influences on age-related changes in the ability to identify blended foods. *Journal of Gerontology*. 1985; 40:47–52. [PubMed: 3965560]
- Murphy C, Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM. Prevalence of olfactory impairment in older adults. *Journal of the American Medical Association*. 2002; 288:2307–2312. [PubMed: 12425708]
- Naessen R. An enquiry on the morphological characteristics and possible changes with age in the olfactory region of man. *Acta Oto-Laryngologica*. 1971; 71:49–62. [PubMed: 5100075]
- Nakashima T, Kimmelman CP, Snow JB Jr. Structure of human fetal and adult olfactory neuroepithelium. *Archives of Otolaryngology*. 1984; 110:641–646. [PubMed: 6477257]
- Neale, M.; Boker, SM.; Xie, G.; Maes, HH. *Statistical modeling*. 6th ed.. Richmond, VA: Department of Psychiatry, Medical College of Virginia; 2003.
- Neale, M.; Cardon, L. *Methodology of Genetic Studies of Twins and Families*. Dordrecht: Kluwer; 1992.
- Nybo H, Gaist D, Jeune B, Bathum L, McGue M, Vaupel JW, et al. The Danish 1905 cohort: A genetic-epidemiological nationwide survey. *Journal of Aging and Health*. 2001a; 13:32–46. [PubMed: 11503846]
- Nybo H, Gaist D, Jeune B, McGue M, Vaupel JW, Christensen K. Functional status and self-rated health in 2,262 nonagenarians: The Danish 1905 Cohort Survey. *Journal of the American Geriatrics Society*. 2001b; 49:601–609. [PubMed: 11380754]

- Nybo H, Petersen HC, Gaist D, Jeune B, Andersen K, McGue M, Christensen K. Predictors of mortality in 2,249 nonagenarians—the Danish 1905-Cohort Survey. *Journal of the American Geriatrics Society*. 2003; 51:1365–1373. [PubMed: 14511155]
- Olofsson JK, Nordin S, Wiens S, Hedner M, Nilsson LG, Larsson M. Odor identification impairment in carriers of ApoE-varepsilon 4 is independent of clinical dementia. *Neurobiology of Aging*. 2010; 31:567–577. [PubMed: 18619712]
- Rabin MD, Cain WS. Odor recognition: Familiarity, identifiability, and encoding consistency. *Journal of Experimental Psychology: Learning, Memory, & Cognition*. 1984; 10:316–325.
- Schiffman SS. Taste and smell losses with age. *Boletin - Asociacion Medica de Puerto Rico*. 1991; 83:411–414. [PubMed: 1807278]
- Segal NL, Topolski TD, Wilson SM, Brown KW, Araki L. Twin analysis of odor identification and perception. *Physiology and Behavior*. 1995; 57:605–609. [PubMed: 7538679]
- Smutzer, GS.; Doty, RL.; Arnold, SE.; Tojanowski, JQ. Olfactory system neuropathology in Alzheimer's Disease, Parkinson's Disease, and Schizophrenia. In: Doty, RL., editor. *Handbook of Olfaction and Gustation*. 2nd ed.. New York: Marcel Dekker; 2003. p. 503-523.
- Walk HA, Johns EE. Interference and facilitation in short-term memory for odors. *Perception & Psychophysics*. 1984; 36:508–514. [PubMed: 6535095]
- Wilson, DA.; Stevenson, RJ. *Learning to smell: Olfactory perception from neurobiology to behavior*. Baltimore, MD: Johns Hopkins University Press; 2006.
- Wysocki CJ, Beauchamp GK. Ability to smell androstenone is genetically determined. *Proceedings of the National Academy of Sciences of the United States of America-Biological Sciences*. 1984; 81:4899–4902.
- Zhuo JM, Prescott SL, Murray ME, Zhang HY, Baxter MG, Nicolle MM. Early discrimination reversal learning impairment and preserved spatial learning in a longitudinal study of Tg2576 APPsw mice. *Neurobiology of Aging*. 2007; 28:1248–1257. [PubMed: 16828204]

Figure 1. Mean ($\pm$ SEM) odor identification test scores as a function of age and sex. Based upon 10-item smell test. See text for details.

Table 1**Multiple Linear Regression Analysis**

Covariate	Regression coefficient (95% CI)*	p-value
Sex		
- Male (ref. group)	0	—
- Female	0.66 (0.39; 0.92)	<0.001
Age (years)	-0.13 (-0.15; -0.11)	<0.001
Cognitive Score		
- 1st quartile (ref. group)	0	—
- 2nd quartile	0.96 (0.60; 1.33)	<0.001
- 3rd quartile	1.58 (1.23; 1.94)	<0.001
- 4th quartile	1.83 (1.47; 2.19)	<0.001
Smoking		
- Smoker (ref. group)	0	—
- Previous smoker	0.65 (0.32; 0.97)	<0.001
- Never smoker	0.66 (0.31; 1.01)	<0.001

Note. Variables selected using stepwise estimation regression (same results when using forward and backward estimation procedures). Inclusion of the variables social group, self rated health, activity of daily living, hearing, and depression, which were individually statistically significant, changed the regression coefficients only minimally.

Table 2

Univariate Analyses — Age- and Sex-Adjusted

Intraclass correlation		B-SIT score		Cognitive composite					
No. of MZ pairs ^a		90/227		99/249					
No. of DZ pairs ^a		96/526		110/555					
		<i>r</i> (95% CI)		<i>r</i> (95% CI)					
MZ		0.16 [−0.05; 0.35]		0.70 [0.59; 0.78]					
DZ		−0.02 [−0.22; 0.19] [*]		0.31 [0.12; 0.47] ^{**}					
Model fit		B-SIT score		Cognitive composite					
		−2LL	d.f.	AIC	<i>p</i>	−2LL	d.f.	AIC	<i>p</i>
Sat vs. —		4928.71	1113	2702.71	—	5651.75	1076	3499.75	—
ACE vs. Sat		4931.63	1119	2693.63	0.82	5657.20	1082	3493.20	0.49
ADE vs. Sat		4931.25	1119	2693.25	0.86	5657.03	1082	3493.03	0.51
AE vs. ADE		4931.63	1120	2691.63	0.54	5657.20	1083	3491.20	0.68
CE vs. ACE		4932.33	1120	2692.33	0.41	5673.34	1083	3507.34	<0.001
E vs. AE		4933.17	1121	2691.17	0.21	5723.07	1084	3555.07	<0.001
Heritability estimates		No significant heritability (E-model)				<i>a</i> ²		<i>e</i> ²	
						0.70 [0.59; 0.77]		0.30 [0.23; 0.41]	

Note. Best fitting model in bold.

^aComplete pairs (i.e. both twins have a score)/broken pairs (i.e. only one twin has a score).

^{*}*p* = .25.

^{**}*p* < .001.

Table 3

Bivariate Analyses (AE-Model); Age- and Sex-Adjusted

Heritability estimates (95% CI)			
B-SIT score		Cognitive composite	
a^2	e^2	a^2	e^2
0.13 [0.01; 0.31]	0.87 [0.69; 0.99]	0.69 [0.58; 0.77]	0.31 [0.23; 0.42]
Genetic and phenotypic correlation			
Phenotypic correlation: 0.33 [0.28; 0.38]		Genotypic correlation: $r_g = 0.64$ [0.19; 1.00]	

Note. Number of twin pairs with both odor identification and a cognitive composite score: MZ: 88 complete (i.e. both twins have scores) and 223 broken (i.e. only one twin has scores); DZ: 91 complete and 507 broken pairs.