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Corresponding Author
Hitesh Jani,
Department of Physiology, AIIMS Bilaspur, Himachal Pradesh, India
janidreams9@yahoo.com

Author Designation
[1]Additional Professor
[2,3]Assistant Professor
[4]Senior Resident
[5]Professor

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Age and Hormone Related Variability in Olfactory Threshold: Cost Effective Quantitative Olfactometry

[1]Punam Verma, [2]Hitesh Jani, [3]Priti Bhanderi, [4]Prashant Kumar Saini and [5]Rupali Parlewar
[1,5]Department of Physiology, AIIMS Bilaspur, Himachal Pradesh, India

Abstract
The sense of smell, known as olfaction, exhibits a significant age-related dependency, with older individuals often experiencing diminished olfactory abilities. These impairments are typically viewed as irreversible and can profoundly impact quality of life, dietary behaviours, and serve as warning signs for mortality, cognitive decline, and dementia. This study assessed age and hormone related variability in the olfaction in terms of detection (olfactory threshold) and discrimination (identification). Total of 150 subjects comprising 75 males and 75 females aged 20-70 years were recruited for the study. The subjects underwent cost effective olfactometry testing for five primary odourants, and their olfactory thresholds for detection and discrimination were recorded. Results showed that older adults have higher odour detection thresholds compared to younger adults. Females at all ages have lower olfactory threshold as compared to males and the threshold is lowest in follicular phase of menstrual cycle and highest in luteal phase. No significant difference was observed in olfactory threshold between odour detection and odour discrimination. These findings contribute to our understanding of olfactory function variability with age and hormones and its potential implications for health and quality of life with the use of cost effective olfactometry.

INTRODUCTION

Human sense of smell, often overshadowed by its flashier counterparts-vision and hearing-plays a surprisingly critical role in our daily lives. Olfaction goes beyond simply detecting pleasant or unpleasant aromas., it influences our perception of taste, steers us clear of hazards like smoke and spoiled food and even shapes our emotional responses[1]. Significance of olfaction in nutrition and social relationships emphasizes its contribution to overall well-being[2].

Sensation of smell is unique in characteristic features like odour detection (which refers to the ability to simply recognize the presence of an odour which requires the stimulation of a single type of olfactory receptor) and odourdiscrimination (This involves identifying a specific odourant, which necessitates the stimulation of multiple receptor types). A normal person can identify as many as thousands of odourants. For odour, molecules to be detected need to dissolve in the mucus lining our nasal cavity. Here, they bind with odourant-binding proteins (around 18k Da in size). This complex then interacts with one of the estimated 1,000 different olfactory receptors we possess[3]. Each receptor can respond to multiple odourants and a single odourant can stimulate several receptors. This intricate interplay generates unique patterns of neural activity in the brain based on the specific odourant, allowing us to distinguish between the vast array of smells we encounter[4].

The applications of olfaction extend beyond the realm of human biology. It serves as a vital tool in various fields, from ensuring food and beverage quality to potentially aiding in illness detection[5,6]. However, the sense of smell is not without its downsides. While not typically a health hazard, strong odours can induce physiological symptoms like respiratory problems, nausea and headaches and even cause psychological stress[7]. Most concerning is the impact of olfactory impairments which is often irreversible, these impairments can significantly affect food choices and have been linked to cognitive decline, dementia and even an increased mortality risk in older adults[8].

Despite its undeniable importance, the complex interplay between age, hormones and olfactory function remains a puzzle in sensory neuroscience. While some studies suggest an inevitable decline in odour perception with age, others present a more nuanced picture[9]. Additionally, hormonal fluctuations, particularly those associated with the menstrual cycle and menopause in females add another layer of complexity to this sense[10,11].

Several studies have explored olfactory thresholds using various methods[12,13,14]. However, these methods often suffer from limitations such as high cost, complexity, or the need for extensive practice. The methodology employed in this study offers a simpler, reliable and satisfactory alternative[15].

By exploring these areas, the efforts are made to shed light on the intricate interplay between aging, hormonal changes and the olfactory system.

Hypotheses: This study had delved into two key areas:

- **The Effects of Aging:** It was hypothesized that older adults exhibit a decline in both odour detection and discrimination abilities compared to younger participants.
- **The Influence of Hormones:** Within the young adult group, we anticipate variations in odour perception based on the gender and hormonal fluctuation during menstrual cycle phase.

Research Question: How do age, gender and hormonal fluctuations affect odour detection and discrimination abilities

Aim and Objectives: To investigate the effects of age, gender and hormonal fluctuations on odour perception using a cost-effective quantitative olfactometry approach.

- To measure odour detection and discrimination thresholds in healthy subjects of 20-70 years of age.
- To find out gender variation and effect of hormonal fluctuation on odour detection and discrimination thresholds in reproductive age group and postmenopausal females.

MATERIALS AND METHODS

Study Design: A quasi-experimental cross-sectional study was conducted with 150 apparently healthy subjects aged 20-70 years. Participants were divided into male and female groups (n=75 each), with further subgroups (Group I, II, III, IV, V) based on age (20-30, 30-40, 40-50, 50-60, 60-70 years respectively).

Inclusion and Exclusion Criteria: Subjects beyond 20-70 year with a history of hormone imbalance, hormone therapy, rhinitis, or other otorhinolaryngological pathologies affecting olfaction were excluded.

Ethical approval from Institute ethical committee and informed consent were obtained before the study commenced.

Odorants and Olfactometry: Five primary odorants were selected: putrid (asafoetida, 10%), camphrous (camphor, 20%), pungent (formalin, 10%), minty (peppermint, 20%) and floral (rosewater, Dabur). A quantitative olfactometry apparatus was used to assess olfactory thresholds. The apparatus consisted of a glass bottle with inlet and outlet tubes, where air was

injected into the bottle to release the odour through the outlet tube into the test nostril.

Procedure: Both nostrils were tested sequentially, with the right nostril tested first. Air was incrementally injected and subjects indicated first for the detection and then identification of the odour. The volume of air (ml) required to detect and identify the odour was recorded as the olfactory threshold for detection and discrimination respectively. The procedure was repeated for all odorants with a gap of 5 minutes in between for each odour to be tested.

In reproductive age group females, 20-45yrs of age (perimenopausal females were excluded) the test was performed three times on specific days of their menstrual cycle (3rd, 10^{th}, 21^{st}). Menstrual cycle was expressed in terms of menstrual phase (day 1-5), follicular phase (day 6-14) and luteal phase (day 15-28) for this study. Those females who had menopause 5 years before were included in menopausal age group females.

Statistical Analysis was performed by using SPSS software version 27

RESULTS AND DISCUSSION

General Linear Model using Multivariate analysis showed 75 subjects in each male and female group and 30 subjects in each age based sub groups (Table 1).

Box's Test of Equality of Covariance Matrices (Intercept-gender+age+gender*age) showed statistical significant variance in olfactory threshold across groups ($F_{(1.4and19805.24)}$=1.411, p-value .001) rejecting the Null hypothesis (Table 2)

Olfactory threshold measured from right and left nostril showed no statistical significant difference, hence mean of the two readings was taken as final olfactory threshold for that odorant.

Odour Detection:

Effect of Age on Olfactory Threshold for Odour Detection: Descriptive study showed the mean and standard deviation of olfactory threshold in each subgroup of both, male and female groups. It was observed that females have lower olfactory threshold for all odorants in all sub groups in comparison to all sub groups of male subjects. It was also observed that olfactory threshold was minimum in 20-30yrs sub group in both male and female subjects and maximum in 60-70yrs sub group in both male and female subjects (Table 3).

Multivariate analysis of olfactory threshold in male and female subjects in all age groups showed statistically significant effect of age and gender on the olfactory threshold (Table 4).

- Statistically significant effect of age on olfactory threshold for all five odourants($F_{4\,(asa),\,139}$=10.927, p<001., $F_{4\,(mint),\,139}$=17.811, p<001., $F_{4\,(camph),\,139}$= 3.278, p<001., $F_{4\,(flor),\,139}$=8.410, p<001., $F_{4\,(pung),\,139}$ =14.872, p<001)
- Statistically significant effect of gender on olfactory threshold only for Mint and pungent odourants ($F_{1\,(asa),\,139}$ .029, p=.865., $F_{1\,(mint),\,139}$=5.176, p=.0241., $F_{1\,(camph),\,139}$=.466, p=.496., $F_{1\,(floral),\,139}$=2.493, p=.1171., $F_{1\,(pung),\,139}$=5.771, p=.018)
- Statistically significant effect of age and gender on olfactory threshold of five different odourants ($F_{4\,(asa),\,149}$=2.515, p=.044., $F_{4\,(mint),\,149}$=5.626, p=<.001., $F_{4\,(camph),\,149}$=3.384, p=.01., $F_{4\,(floral),\,149}$=5.484, p=<.001., $F_{4\,(pung),\,149}$=4.568, p=.002).

Post Hoc Test (Bonferroni) was used to analyze intergroup comparison of olfactory threshold in different age groups (Table 5). Statistically significant difference was found between GroupI/GroupII and Group IV and Group V for all odourants.

Olfactory Threshold in Reproductive and Menopausal Female: In Group III and IV, 15 females were in perimenopausal phase so they were not included to analyze the difference between olfactory threshold of reproductive females and menopausal females. Out of total Seventy five females, sixty females (Thirty reproductive females from 20-45 years of age and thirty menopausal females from 55-70 years of age) were included in the following analysis.

Univariate analysis showed that reproductive age group females have statistically significant lower olfactory threshold for all odorants in comparison to menopausal females (Table 6 and 7).

Olfactory Threshold in Different Phases of Menstrual Cycle: Univariate analysis was performed to analyze the olfactory threshold of reproductive age group females in different phases of menstrual cycle for all five odorants. Statistically significant difference was found in olfactory threshold in female at different phases of menstrual (Table 8). It was observed that olfactory threshold was lowest during follicular phase was followed by luteal phase and was maximum in menstrual phase (Table 9). Multiple comparisons amongst different phases of menstrual cycle showed statistically significant difference in olfactory threshold among all phases. (Table 10).

Odour Discrimination: Unpaired t Test was used to compare olfactory threshold for odour detection and odour identification in different age groups. No statistical significant difference was observed between olfactory threshold for Odour detection and odour

Table 1: Between-Subjects Factors

		N
Gender	Female	75
	Male	75
Age	20-30	30
	30-40	30
	40-50	30
	50-60	30
	60-70	30

Table 2: Box's Test of Equality of Covariance Matrices[a]

Box's M	223.131
F	1.411
df1	135
df2	19805.245
Sig.	.001

Tests the null hypothesis that the observed covariance matrices of the dependent variables are equal across groups.

α. Design: Intercept + Gender + age + Gender * age

Table 3: Mean ± Sd of Olfactory Threshold In different age groups for all five odorants

	Asafoetida		Mint		Camphor		Floral		Pungent		Total
Sub groups	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female+Male
	n=15	n=15	n=15	n=15	n=15	n=15	n=15	n=15			N=150
20-30yrs (n=30)	3.33 ±1.24	3.6 ±1.50	3.46 ±1.76	3.8±1.37	2.93 ±2.60	3.46 ±1.30	6±3.85	4.6±1.68	3.06±1.98	4.8±2.36	3.9±2.05
30-40 yrs.(n=30)	3.86±1.92	3.86±1.92	3.86±2.44	4.13±1.92	4.26±3.28	3.73±1.94	3.53±1.72	5±2.23	5.06±3.10	4.73±2.81	4.20±2.34
40-50 yrs.(n=30)	5.33±1.63	4±1.69	6.8±1.47	4.4±2.41	5.2±1.47	4.2±1.58	7.33±1.79	7.2±3.68	6.8±1.26	4.06±2.05	5.53±2.13
50-60 yrs.(n=30)	5.73±1.66	5.6±6.86	6.86±0.99	5.86±1.76	5.6±1.54	5.26±1.48	7.86±2.06	5.33±1.23	7.86±2.19	6.06±1.70	6.20±1.73
60-70 yrs.(n=30)	6.6±1.05	6.86±1.72	7.33±1.23	6.8±1.97	5.66±1.17	7.33±1.49	7.8±1.89	7.4±1.50	8.13±1.72	7.06±1.48	7.1±1.59
Total (N=150)	4.97±1.92	4.78±2.02	5.66±2.31	5±2.19	4.73±2.35	4.8±2.08	6.50±2.858	5.90±2.47	6.18±2.82	5.34±2.34	5.39±2.35

Table 4: Multivariate Analysis to assess the effect of age and gender on olfactory threshold for odour detection

Effect		Value	F	Hypothesis df	Error df	Sig.
Intercept	Pillai's Trace	.974	1006.204[b]	5.000	136.000	.000
	Wilks' Lambda	.026	1006.204[b]	5.000	136.000	.000
	Hotelling's Trace	36.993	1006.204[b]	5.000	136.000	.000
	Roy's Largest Root	36.993	1006.204[b]	5.000	136.000	.000
Gender	Pillai's Trace	.080	2.354[b]	5.000	136.000	.044
	Wilks' Lambda	.920	2.354[b]	5.000	136.000	.044
	Hotelling's Trace	.087	2.354[b]	5.000	136.000	.044
	Roy's Largest Root	.087	2.354[b]	5.000	136.000	.044
Age	Pillai's Trace	.782	6.761	20.000	556.000	.000
	Wilks' Lambda	.300	9.888	20.000	452.011	.000
	Hotelling's Trace	2.061	13.858	20.000	538.000	.000
	Roy's Largest Root	1.922	53.438°c	5.000	139.000	.000
Gender * Age	Pillai's Trace	.329	2.491	20.000	556.000	.000
	Wilks' Lambda	.703	2.537	20.000	452.011	.000
	Hotelling's Trace	.380	2.554	20.000	538.000	.000
	Roy's Largest Root	.222	6.180°c	5.000	139.000	.000

Table 5: Post Hoc Test (Bonferroni) to compare olfactory threshold for odour detection in different age groups

Group I	Group II	-0.3	.24862	.095
	Group III	-1.63	.24862	1.000
	Group IV	-2.3	.24862	.004
	Group V	-3.2	.24862	.000
Group II	Group I	-0.3	.24862	.095
	Group III	-1.33	.24862	.001
	Group IV	-2.0	.24862	.000
	Group V	-2.9	.24862	.000
Group III	Group I	-1.63	.24862	1.000
	Group II	-1.33	.24862	.001
	Group IV	-0.67	.24862	.345
	Group V	-1.57	.24862	.000
Group IV	Group I	-2.3	.24862	.004
	Group II	-2.0	.24862	.000
	Group III	-0.67	.24862	.345
	Group V	-0.9	.24862	.000
Group V	Group I	-3.2	.24862	.000
	Group II	-2.9	.24862	.000
	Group III	-1.57	.24862	.000
	Group IV	-0.9	.24862	.000

Table 6: Mean ± Sd of Olfactory Threshold In Reproductive And Menopausal Females

	Asafoetida	Mint	Camphor	Floral	Pungent	Total
Reproductive females(n=30)	3.67±1.27	4.86±3.14	3.6±1.61	4.07±2.75	3.60±2.9	3.96±2.61
Menopausal females (n=30)	5.53±1.63	6.32±1.84	5.24±1.36	7.17±1.90	5.33±1.42	5.60±1.89
Total (n=60)	4.60±2.12	5.59±2.84	4.42±2.31	5.62±2.97	4.45±2.48	4.78±2.63

Table 7: Univariate Analysis for comparison of olfactory threshold for odour detection in reproductive and menopausal females

Dependent Variable:	olfactory Threshold				
Source	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Corrected Model	699.147[a]	9	77.683	16.452	.000
Intercept	8363.520	1	8363.520	1771.242	.000
Females (Reproductive and Menopausal)	522.720	1	522.720	110.703	.000
odour	128.880	4	32.220	6.824	.000
Females * odour	47.547	4	11.887	2.517	.042
Error	1369.333	290	4.722		
Total	10432.000	300			
Corrected Total	2068.480	299			

Table 8: Univariate Analysis for comparison of olfactory threshold for odour detection in different phases of menstrual cycle

Dependent Variable:	olfactory threshold					
Source		**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Intercept	Hypothesis	2135.707	1	2135.707	18.315	.043
	Error	256.268	2.198	116.607a		
Phases	Hypothesis	222.253	2	111.127	75.255	.000
	Error	11.813	8	1.477b		
odour3	Hypothesis	27.827	4	6.957	4.711	.030
	Error	11.813	8	1.477b		
Phases * odour3	Hypothesis	11.813	8	1.477	1.381	.210
	Error	144.400	135	1.070c		

Table 9: Mean ± Sd of Olfactory Threshold in different phases of menstrual cycle

	Asafoetida	**Mint**	**Camphor**	**Floral**	**Pungent**	**Total (n=50)**
Menstrual (n=10)	5.1±1.32	6.16±4.41	5.1±1.79	4.35±2.86	4.80±2.9	5.10±2.65
Follicular (n=10)	1.84±0.68	3.36±2.69	2.01±1.78	3.10±2.68	1.80±3.10	2.42±2.18
Luteal (n=10)	4.06±1.81	5.16±2.32	3.60±1,26	4.76±2.71	4.20±2.71	4.35±2.16
Total (n=30)	3.67±.1.27	4.86±3.14	3.60±1.61	4.07±2.75	3.60±2.9	3.96±2.33

Table 10: Post Hoc Test (Bonferroni) to compare olfaction in different phases of menstrual Cycle

Age Groups	**Odour Detection**	**Odour discrimination**	**p-value**
20-30yrs (n=30)	3.9±2.05	3.93±2.65	.342
30-40 yrs. (n=30)	4.20±2.34	4.20±2.12	.00
40-50 yrs. (n=30)	5.53±2.13	5.53±1.76	.00
50-60 yrs. (n=30)	6.20±1.73	6.89±1.23	.067
60-70 yrs. (n=30)	7.10±1.59	8.62±1.43	0.01

Table 11: Comparison of Olfactory Threshold for odour detection and odour discrimination in different age groups

		Mean Difference	**Std. Error**	**Sig.**
Menstrual	Follicular	2.68*	.20685	.000
	Luteal	.75	.20685	.004
Follicular	Menstrual	2.68*	.20685	.000
	Luteal	-1.93*	.20685	.000
Luteal	Menstrual	-.7000*	.20685	.004
	Follicular	2.1600*	.20685	.000

discrimination in all groups except in Group V in which statistically significantly lower olfactory threshold for odour detection was observed in comparison to that of odour discrimination (Table 11).

Our sense of smell, like other sensory systems, undergoes a fascinating transformation with age. This decline in olfactory function, however, transcends a simple loss of sensory acuity. It has unique causes and consequences, affecting not just our health and well-being, but also our behaviour due to the intricate connections between the olfactory system and the limbic system and reticular formation, brain regions involved in emotion, memory and arousal.

The observed rise in olfactory thresholds with advancing age in the present study provides compelling evidence for this decline. This aligns the previous studies that documented a significant increase in olfactory impairment prevalence with age[16,17]. While this study focused on individuals below 70, the existing literature suggests a further decrease in sensitivity and odour identification ability in older age groups (70-80 years)[18,19]. No age related olfactory decline was observed in animals[20]

It is important to acknowledge that age is not the sole culprit in this olfactory function. Environmental exposures, sinus issues and smoking also play a role, potentially affecting the peripheral or central olfactory pathways[21]. These factors can contribute to a decline in olfactory threshold, adding complexity to the aging narrative.

The underlying mechanisms responsible for this decline appear to be a combination of structural and functional changes. Structural factors include the degradation of olfactory epithelium, receptor cells and neural pathways. Functional factors encompass alterations in nasal mucus composition, reduced blood flow, and changes in neurotransmitters and neuromodulatory systems[19,20]. This aligns with the

established role of specific neurotransmitters in functions like arousal, attention and memory, functions known to decline with age[23].

The Gender Divide: A Hormonal Influence: This study revealed a significant gender difference in olfactory thresholds, with females across all age groups demonstrating a superior sensitivity. This echoes findings by Doty and Cameron (2003) who reported better olfactory performance in women[24]. Potential explanations for this disparity include:

Cognitive vs. Perceptual Differences: While the underlying neural circuitry for olfaction is similar in both sexes, women might excel at the cognitive processing of olfactory information[25].
The Role of Gonadal Hormones: The presence of gonadal hormones, particularly estrogen, may enhance olfactory function in females[26].

Estrogen's Impact on the Olfactory Neuroepithelium: Estrogen might directly influence the olfactory neuroepithelium, the tissue responsible for odour detection[26].

Furthermore, this study observed variations in olfactory thresholds across the menstrual cycle, with the lowest thresholds occurring during the follicular phase (when estrogen levels are high) and the highest thresholds during menstruation (when estrogen levels are low). This aligns with previous researches that documented similar fluctuations in olfactory sensitivity with hormonal changes[27,28].

The observed decline in olfactory function after menopause further strengthens the link between sex hormones and olfaction[29,30]. The significant decrease in olfactory ability post-menopause could be attributed to the decline in sex hormones, as hormone replacement therapy has been shown to improve olfactory sensitivity in postmenopausal women. The reduced estrogen levels after menopause might impact neuronal plasticity and conduction time within the olfactory system[31].

Odour Discrimination: Statistically significantly, lower olfactory threshold for odour detection in comparison to that of odour discrimination in subjects of 60-70yr of age while no significant difference in 20-60yrs subjects suggested that detection, a purely sensory process, relies primarily on the peripheral olfactory system. In contrast, odour discrimination, which involves both sensory and cognitive processes, might be more susceptible to age-related declines in cognitive function, particularly alertness, which can lead to indecisiveness in odour identification tasks[32,33].

CONCLUSION

Sense of smell undergoes a remarkable transformation with age, influenced by a complex interplay of biological and environmental factors. While the decline in olfactory function with age is undeniable, the underlying mechanisms are multifaceted. Further research is needed to fully understand the role of hormonal fluctuations, neurotransmitter changes and the intricate link between the olfactory system and brain regions involved in memory and cognition. Unravelling these mysteries will not only enhance our understanding of healthy aging but also potentially pave the way for interventions to preserve or improve olfactory function throughout life.

The COVID-19 pandemic highlighted the prevalence of olfactory loss and dysfunction commonly following a COVID-19 diagnosis. This study suggests cost-effective olfactometry to identify olfactory impairments in post covid patients

Limitations and Future Directions: While this study sheds light on the potential effects of age and hormones on olfaction, there are limitations to consider:

Sample Size: A formal sample size calculation was not performed to determine the minimum number of participants required for statistically robust results. This limits the generalizability of our findings to larger populations.

Hormonal Assessment: Due to limited resources, we were unable to directly measure hormonal levels in female participants. This additional data would have strengthened the link between hormonal fluctuations and odour perception.

Methodology Validation: The cost-effective olfactometry method employed here requires further precision and validation against established techniques. While the results align with previous studies, broader acceptance would necessitate comparisons with gold-standard methods.

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