Effect of gender on odor identification at different life stages: a meta-analysis*

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Abstract

Background: Although conflicting findings abound, gender-related differences in olfactory identification have received continuous attention. To our best knowledge, no systematic and quantitative research has examined gender differences in olfaction identification at various stages of life. The present study aimed to find out if there is gender difference in human olfaction identification in different life stages.

Methodology: Studies cited in the PubMed database were searched from its inception to August 2017 using the terms "olfact*" or "smell" and "gender" or "sex". The effect size of each comparison was calculated. 24 studies were included in this meta-analysis.

Results: In this meta-analysis, we used Cohen's d to determine the effects sizes for the comparisons between women versus men among different groups. Its value was 0.18 (95% CI: -0.13 to 0.49) in Group A (age<18years), 0.62 (95% CI: 0.43 to 0.81) in Group B (age 18-50years), and 0.33 (95% CI: -0.01 to 0.66) in Group C. The effect was considered relatively small in Group A (age<18years) and Group C (age>50years), and a medium effect in Group B (age18-50 years). Moreover, a significant difference was only present in Group B (age18-50 years). Summarizing, the gender effect was only present in the group aged 18-50 years, in which women outperformed men significantly in odor identification.

Conclusions: This meta-analytic review indicated that the gender differences only exist in young adults (age18-50 years), while absent in juveniles (age<18years) or an aged cohort (age >50years). Females outperformed males in the young adults.

Key words: odor identification, gender effect, life stages

Introduction

Investigation of gender differences in olfaction is of great interest. First reported in the late 1800's [1], gender-related differences in olfactory function have received continuous attention, although conflicting findings abound, especially from those studies adopting psychophysical olfaction tests. Most studies have shown that the olfactory system in the human brain is sexually dimorphic [2-9]. However, a few studies reported no gender differences in overall percentage of gray or white matter in brain areas involving olfactory processing [10]. Examination of electrophysiological measures consistently show different odor event-related potentials between females and males, with a larger amplitude and shorter latency of the P2 component in women compared with those in men [11-14]. At the behavioral level, most studies have demonstrated that women outperform men in olfactory function, especially in odor identification [15,16], but there are also numerous studies that did not find an effect of gender on odor identification [17-20]. Doty et al. [21] reported that a gender effect existed across all age categories, whereas many studies did not find gender differences present at different life stages. For example, Laing et al. [22] suggested that there were no significant gender differences in odor identification between

girls and boys aged 5–7 years, and others have also indicated no gender effect for odor identification, discrimination, or threshold in participants under 18 years of age [23-25]. A growing body of evidence also indicates that olfactory performance differences are not significant between older females and males [26-28]. This is consistent with the results of some other studies examining difference across life stages, that is, from prepubertal to elderly participants or from young to elderly adults, that found no significant gender differences [29-32].

These conflicting outcomes indicate that a meta-analysis is warranted to systematically and quantitatively examine gender differences in olfaction at various stages of life. However, to the best of our knowledge, no such meta-analysis has yet been reported. Among the psychophysical measures of olfactory performance, the most widely used is odor identification, which is considered to be a central aspect of olfaction and requires higher-order brain processing [33]. Thus, the goal of the present meta-analysis was to examine whether a significant gender difference exists in odor identification across three life stages (children and adolescents, <18 years old; younger adults, 18–50 years; older adults, >50 years).

Materials and methods

Search strategy

A literature search of the PubMed database (https://www.ncbi.nlm.nih.gov/pubmed) was conducted by searching studies published from inception until August 2017. The search terms used included "olfact*" or "smell," and "gender" or "sex." A thorough manual review was conducted of studies cited in retrieved review articles for potential inclusion in the present meta-analysis.

Study selection

The selected studies were those that were published in the English language, used living participants, and were consistent with the following four criteria: 1) Studies that included participants who are neurologically healthy and without olfactory disorders were included. However, studies whose participants were judged to overlap with others were excluded. 2) Studies that used psychophysical measure of olfactory identification were included. Studies that collected other data (e.g., electrophysiological or neuroimaging data) but were without or with low validity psychophysical measures of olfactory identification data were excluded. By low validity, we meant studies adopting home-made odors without standardized procedure other than employed any of the measurement summarized by Thomas-Danguin [34]. 3) Studies that grouped participants according to the following age groups were included: children or adolescents group comprising individuals <18 years of age; a younger adult group with individuals 18–50 years old; an older adult group that included individuals older than 50 years. The separation of the two adult groups at 50 years old is based on the results of a meta-analysis by Zhang and Wang [35] showing that odor identification in humans starts to decline at the age of 50. Studies that did not separate the participants according to these three life stages were excluded. 4) Studies that included both female and male participants and reported their raw data were included. Studies that included only females or males were excluded. Because of the small number of published studies examining children and adolescent participants, the authors of those studies who did not list raw female and male data were contacted, and these data were requested for the present meta-analysis. Published studies examining individuals in the two adult groups without separate raw data reported were excluded.

Data extraction

The following information was extracted for meta-analyses: 1) demographic characteristics of the study cohort (e.g., sample size, gender, and country); 2) the psychophysical tools used to determine olfactory identification function; 3) the mean and standard deviation of the odor identification score. For cases in which the means and standard deviations (SDs) were not indicated in the article, either the SD was calculated from the Standard Error of the Mean (SEM) using the formula provided by Streiner [36], or the authors were contacted and the missing data were obtained. Data transfer was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions [37].

Outcome

The outcome was the effect sizes of the comparisons between female and male participants in the three aforementioned groups: children and adolescents (<18 years), younger adults (18–50 years), and older adults (>50 years).

Statistical analysis

The statistical analyses were conducted with Review Manager (RevMan) version 5.3 software. The odor identification score was considered a continuous variable, and the effect size was computed using the mean and SD, Cohen's d was used to represent effect size. To control for different standard deviation during effect size computing, RevMan calculates a weight for each study (for continuous outcomes this is based on the standard deviation of the study, the smaller the standard deviation, the greater the weight). This determines how much each individual study contributes to the pooled estimate. The analyses were conducted for the three groups described in the section titled Study selection. For all included studies, the individual and overall effect sizes, individual and overall 95% confidence intervals (CIs), weight of each study, and test for overall effect Z value were calculated.

The I-squared statistic, a measure of the heterogeneity of the selected studies was used, and a significant and substantial heterogeneity was assumed to exist if the value was greater than

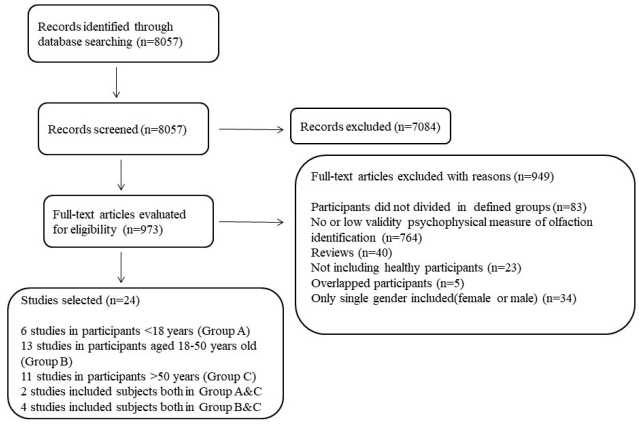

Figure 1 Selection flowchart.

50% [38], whereas a value of the I-squared statistic less than 50% meant no significant and substantial heterogeneity. A random-effects model was used when the heterogeneity was judged to be significant; otherwise a fixed-effects model was used in the present meta-analysis.

Results

The database search yielded 8057 potential entries. Following a review of the title and abstract for all of these articles, the full text of 972 articles was examined in detail. The criteria defined in the present study section titled Study selection were applied, by now only 20 articles were included. When we emailed the corresponding authors of potential papers to share data, another 6 studies were included. At last 24 articles were included (see selection flowchart in Figure 1). The studies [16,19,20,28,39-58] included for each of the three groups are shown in Table 1.

Demographic characteristics and measures used in odor identification

Table 1 showed the demographic characteristics of participants and measures used in odor identification. The distribution of participants was worldwide, including in Africa, Asia, Europe, and North America.

Odor identification was measured in the selected studies using three procedures: "Sniffin' Sticks" [59,60] and its modified 14-item "Sniffin' Kids" identification tests [41]; the full [61] and briefer versions (B-SIT) [62] of the University of Pennsylvania Smell Identification Test (UPSIT); and the Scandinavian Odor Identification Test (SOIT) [63]. In the Sniffin' Sticks identification test, participants are presented with 16 standardized felt-tip pens that are filled with odors (Burghart Messtechnik Company, Germany). The pens are presented one at a time, and the participants are asked to identify the scent by choosing among four descriptors provided for each pen (four alternative forced choice). The odor identification score ranges from 0 to 16 (correct). The Sniffin' Kids test follows the same procedure as Sniffin' Sticks, but the odors apple and turpentine were excluded to make the test more suitable for children, and the highest correct score is 14. The UPSIT was developed in America and contains 40 common odorants, each of which is embedded in a microcapsule placed on a separate page. The participant identifies the best answer from four items listed as multiple choices displayed on the same page. The score ranges from 0 (no odor correctly identified) to 40 (all odors correctly identified). The B-SIT, a shorter version of the UPSIT, contains only 12 odorants but uses the same procedure as that for the UPSIT, with scores ranging from 0 to 12. The SOIT was developed in Scandinavia and consists of 16 odors, with 4 response alternatives for each; thus, scores range from 0 to 16. It was developed for the Scandinavian population and has displayed satisfactory test-retest and split-half reliability results [63,64].

Overall meta-analysis results

There are 8,112 participants in total, 1,180 (female 52.71%) participants with an age range from 5-18 years in the group under 18 years, 1,130 (female 51.41%) participants with an age range from 18-50 years in the group aged 18-50 years, 5,802 (female 57.03%) participants with an age range from 50-100 years in the group more than 50 years. Most studies were age matched

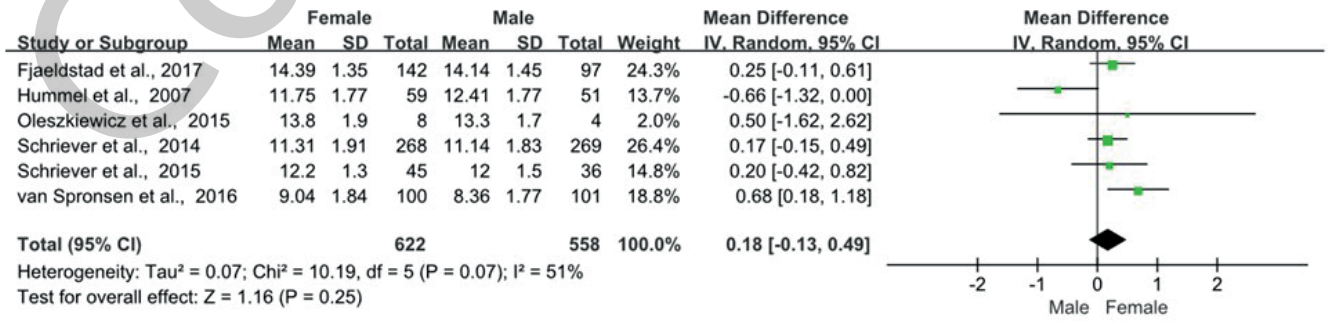

Figure 2. Meta-analysis of studies comparing females and n1ales <18 years old.

Figure 3. Meta-analysis of studies comparing females and males aged 18-50 years.

Studies	Olfactory Test	OI Score of Female (M ± SD)	Female (N)	OI Score of Male (M ± SD)	Male (N)	Country
Studies of comparison between female versus male in Group A (age<18years)						
Fjaeldstad et al., 2017[39]	Sniffin' Sticks*	14.39±1.35	142	14.14±1.45	97	Denmark
Hummel et al., 2007[16]	Sniffin' Sticks#	11.75±1.77	59	12.41±1.77	51	Germany, Australia
Oleszkiewicz et al., 2015[40]	Sniffin' Sticks*	13.8±1.9	8	13.3±1.7	4	Egypt
Schriever et al., 2014[41]	Sniffin' Sticks Kids^	11.31±1.91	268	11.14±1.83	269	Germany
Schriever et al., 2015[42]	Sniffin' Sticks Kids^	12.2±1.3	45	12±1.5	36	Germany
van Spronsen et al., 2013[43]	Sniffin' Sticks^	9.04±1.84	100	8.36±1.77	101	Netherlands
Studies of comparison between female versus male in Group B (age18-50years)						
Altundag et al., 2015[44]	UPSIT*	36.7±2.9	34	34.4±2.8	17	Turkey
Bramerson et al., 2004[45]	SOIT^	14.84±1.21	172	14.2±1.53	177	Sweden
Ekstrom et al., 2017[46]	SOIT^	8.59±1.78	110	7.97±1.79	118	Sweden
Frasnelli et al., 2010[47]	UPSIT^	31.9±3.2	25	30.8±3.1	19	Canada
Houlihan et al., 1994[48]	UPSIT^	37.3±2.8	15	36.9±2	22	USA
Kamath et al., 2008[49]	B-SIT^	10.56±0.96	16	10.2±1.4	10	USA
Kopala et al., 1995[50]	UPSIT^	37.3±1.7	16	36.8±2.5	14	Canada
Novakova et al., 2013[19]	Sniffin' Sticks	13.99±1.24	67	13.55±1.52	88	Czech Republic
Ojima et al., 2002[51]	UPSIT	31.7±4.2	40	28.8±3	10	Japan
Stuck et al., 2006[20]	Sniffin' Sticks^	14.47±1.34	19	13.8±1.74	15	Germany
Yang et al., 2010[52]	Sniffin' Sticks	12.6±1.25	30	12.27±1.33	30	China
Yousem et al., 1999[53]	UPSIT^	38.5±1.1	8	35.7±2.7	8	USA
Yucepur et al., 2012[54]	UPSIT	21.6±4.4	29	21.1±5.1	21	Turkey
Studies of comparison between female versus male in Group C (age>50years)						
Bramerson et al., 2004[45]	SOIT^	13.06±2.77	273	12.52±2.9	243	Sweden
Devanand et al., 2010[55]	UPSIT^	26.6±6.6	749	24.4±7.4	343	USA
Ekstrom et al., 2017[46]	SOIT^	6.93±2.23	774	6.36±2.13	606	Sweden
Hummel et al., 2007[16]	Sniffin' Sticks#	12.06±2.31	251	12.2±2.57	238	Germany, Australia
Liang et al.,2016[56]	Sniffin' Sticks 12	8.02±2.01	964	7.92±2.08	818	China
Liu et al., 2015[57]	UPSIT^	36±2.96	67	35±3.7	121	USA
Oleszkiewicz et al., 2015[40]	Sniffin' Sticks*	11.5±4	6	8.2±3.7	9	Egypt
Seligman et al., 2013[28]	Sniffin' Sticks	12.64±2.44	88	12.39±2.69	44	USA
Sohrabi et al., 2009[58]	Sniffin' Sticks	12.66±2.01	102	12.8±1.79	42	Australia
Stuck et al., 2006[20]	Sniffin' Sticks^	13.8±1.1	20	14.14±0.94	14	Germany
Yang et al., 2010[52]	Sniffin' Sticks	11.53±2.41	15	12.53±1.18	15	China

OI= Olfaction Identification. * The olfactory test had been culture adapted; ^ The olfactory test was used either in the original countries where it had been developed or in the similar ethic groups; #Part of the subjects from Germany and the other from Australia.

between female and male.

For the meta-analysis comparing odor identification in females and males younger than 18 years old, the effect size was 0.18 (95% CI: −0.13 to 0.49). According to Cohen's typology [65], an effect size of 0.18 is small. The test for the overall effect was Z = 1.16 (p = 0.25), indicating no significant difference between the two groups (Figure 2).

For the meta-analysis comparing odor identification in younger adult women and men aged 18–50 years, the effect size as determined using Cohen's d was 0.62 (95% CI: 0.43 to 0.81), considered a moderate effect, and the result for the overall effect test was Z = 6.44 (p< 0.00001), a significant effect (Figure 3).

For the meta-analysis comparing odor identification in older women and men aged over 50 years, the effect size as determined using Cohen's d was 0.33 (95% CI: -0.01 to 0.66), considered a relatively small effect, and the test result for the overall effect was Z = 1.88 (p = 0.06), indicating no significant difference between the two groups (Figure 4).

We also conducted a subdivision comparison between female and male in the age 16-35 [16,19,20,40,45,47,49,52]. However, compared to the age 18-50, the effect size was relatively small (Cohen's d=0.36, 95% CI: 0.18 to 0.54), though a significant difference (Z = 3.87, p=0.0001) was found that female outperformed male in odor identification. To clarify this result, we further explored the comparison between the age 18-35 [19,20, 45,47,49,52], and the result was quite close to group of 18-50, with Cohen's d=0.55 (95% CI: 0.33 to 0.76), the overall effect was Z = 4.91 (p<0.00001) which meant female had significant better odor identification ability than male.

In all, the effect of gender only existed in the group aged 18-50 years, in which female outperformed male significantly in odor identification.

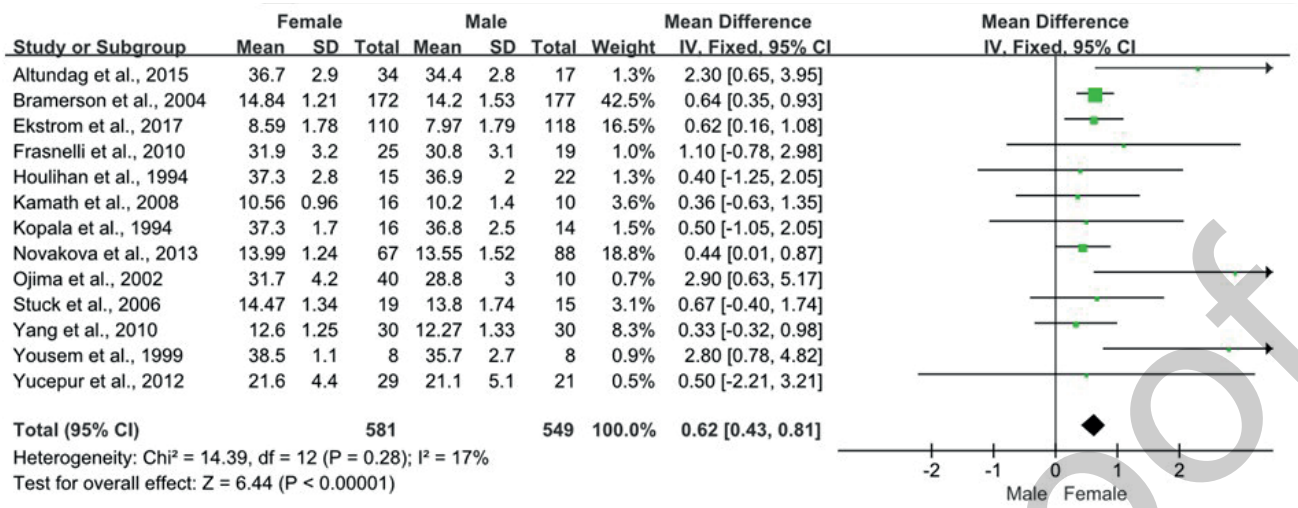

Figure 3. Meta-analysis of studies comparing females and males aged 18-50 years.

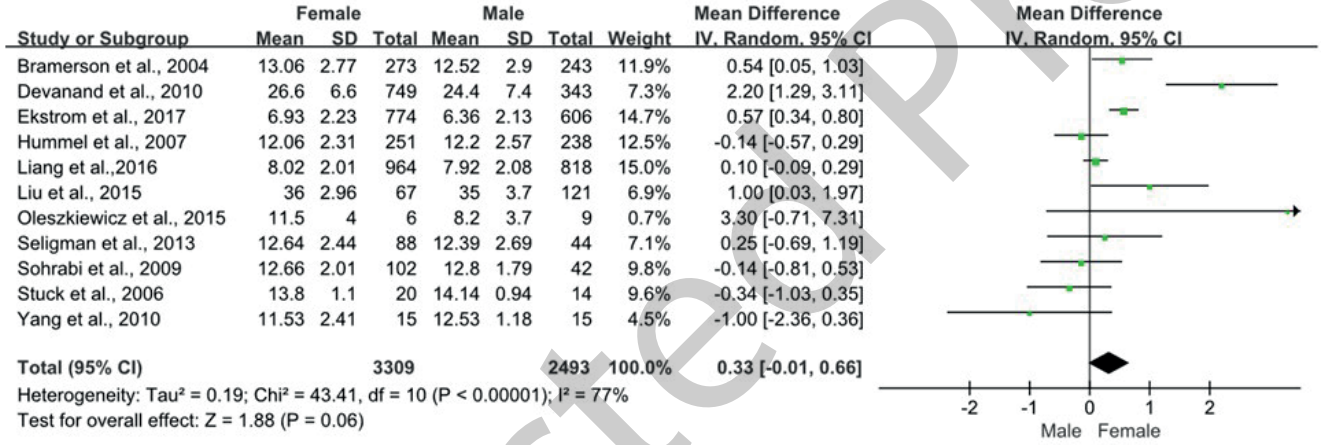

Figure 4. Meta-analysis of studies comparing females and males aged >50 years.

Discussion

This meta-analytic review indicated that significant gender differences for odor identification existed only in younger adults (aged 18–50 years), but not in children and adolescents (<18 years) or older adult (>50 years) participants. Many factors influence and may complicate olfactory function; thus, multiple potential reasons may explain the gender difference revealed here. However, the three most well-established potential explanations are examined here in light of our findings.

The first is the gender difference in gonadal steroid levels, especially estrogen. Hormones affect humans throughout life, before, during, and after puberty. Gonadal steroid hormones or their receptors have been found in the olfactory epithelium, bulb, and other olfactory-related brain regions in several mammalian species [66-69]. Several studies have suggested that androgens depress while estrogens enhance olfactory performance [70-72]. Observing cytological changes in nasal epithelium across the menstrual cycle, Navarrete-Palacios and colleagues [73] suggested that changes in hormone levels could influence olfactory function both peripherally and centrally.

The second mechanism that may contribute to our results is the sexual dimorphism of the innate anatomy and physiology of the olfactory system. Beginning with the peripheral receptor neurons in the nasal cavity and the first relay in the olfactory bulb, olfactory information must be transmitted from peripheral olfactory structures (the olfactory epithelium) to more central structures (the olfactory bulb and cortex) before being projected to the hypothalamus, thalamus, and frontal cortex [74]. The olfactory system is unique among the senses in that it does not use the thalamus as a primary relay center to the cortex and that pathways are ipsilateral [75,76], and details see Figure 5a (reprinted with permission from Martzke et al. [33]) and Figure 5b (reprinted with permission from Duda [77]). Although the entire olfactory system has not been shown to be sexual dimorphic, evidence indicates that the densities of neurons, non-neurons, and total cells in the olfactory bulb are higher in females than males [78]. A positive correlation between olfactory function and olfactory bulb volume is well documented [79-83]. In addition, the volumes

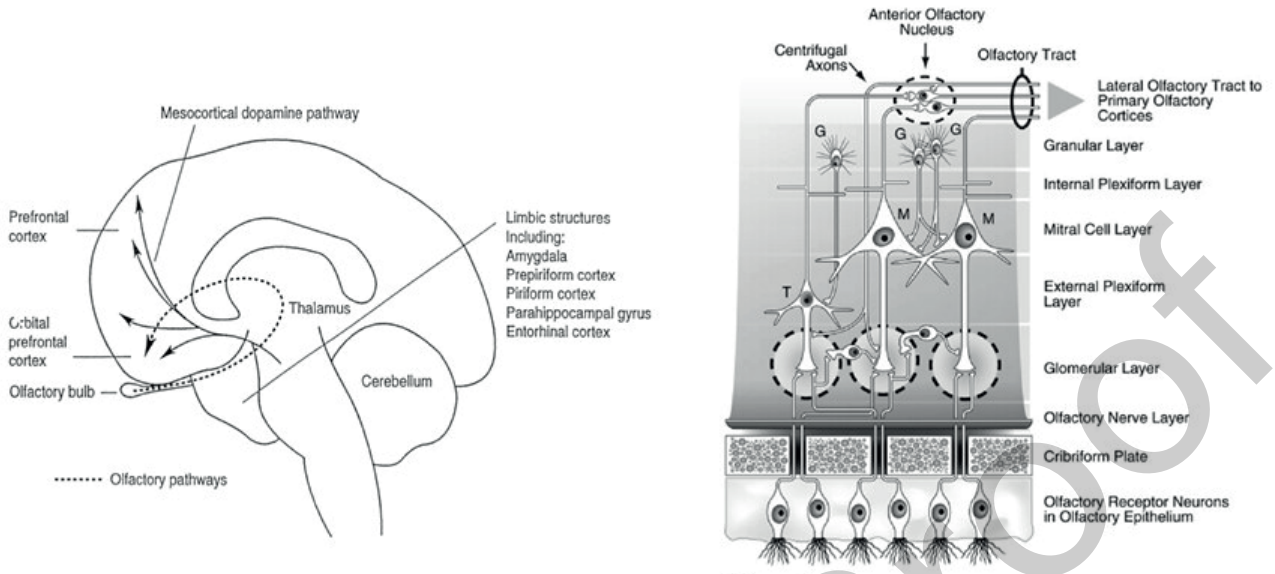

Figure 5. A) Medial view of the brain showing human olfactory pathways. [33] B) Schematic view of olfactory bulb neuroanatomy [77].

of the orbitofrontal cortex Brodmann areas (BAs) 10, 11, and 25 are larger in women than in men [84]. Garcia-Falgueras et al. [2] and Luders et al. [85] also reported that females have a higher proportion of gray matter than males do in these same brain areas (i.e., BA 10, 11, and 25). These areas of the orbitofrontal cortex are considered part of the olfactory system and provide modulatory feedback information to the mammalian olfactory bulb [86,87]. Another brain region that forms part of the olfactory system, the hippocampus, has been shown to be either larger or bilaterally denser in females than in males [88,89].

The third potential contribution to our results in gender differences is olfactory processing. Although chemosensory transmission is likely equal in both genders, the processing of this information in the olfactory bulb differs in men and women. The ability of women to identify and perceive odorants is more accurate than that of men [90,91]. In addition, higher cerebral blood flow and cerebral metabolic rate of glucose use has been observed in women compared with men during olfactory processing [2], which probably means that compared with those in men, female olfactory bulbs transfer a greater amount of excitatory olfactory information to the subsequent cortical regions. This interpretation is consistent with the finding by Oliveira-Pinto and colleagues [78] of a richer neuronal machinery in the olfactory bulbs of women.

Undoubtedly, there are multiple factors that underlie gender dimorphic olfactory performance. If the first plausible mechanism summarized herein, that of differences in gonadal steroid levels, is the primary contribution to our finding of gender-specific olfactory identification in younger adults (aged 18–50 years), one would expect the children and adolescents (<18 years) and older (>50 years) groups to exhibit no marked gender differences in olfaction, since no reproductive hormone differences are present prepuberty [92,93], and estrogen levels decline markedly in older women [94]. This interpretation is consistent with the outcome of present study, that a significant gender difference in odor identification was found only in the group of participants aged 18–50 years, not in the groups with individuals <18 or > 50 years old. Regarding the second and third plausible contributions to our finding, age-related alterations within the olfactory system (e.g., olfactory epithelium, olfactory bulb, and associated brain structures) and olfactory processing (e.g., neurotransmitter deficiencies) are well established; however, the participants providing this evidence were often both females and males [79,95-98]. Little research has been conducted comparing the degree to which gender was associated with these age-related alterations. Thus, gender-age interactions associated with the anatomy and physiology of the olfactory system and with olfactory processing should be further studied in the future.

The present meta-analytic review had a few limitations. First, we conducted a meta-analysis only on one aspect of olfactory function, namely, odor identification, because measures of this aspect are most widely investigated. However, other aspects exist, including sensitivity, discrimination, memory, and hedonism, and should be explored. Second, only six studies were included in the children and adolescents (<18 years old) analysis, as this group has received less attention than that for younger and older adults, potentially limiting the generalizability of our results for entire this population. Third, although we discussed the most investigated primary mechanisms that may contribute to our findings, gender-specific olfactory identification is complex, and we did not test our hypothesis that differences in age-related gonadal steroid levels in males and females may be associated with the significant gender difference we detected

for odor identification in the younger adult group. Last, we combined different test types (e.g., UPSIT and Sniffin' Sticks Test) into one outcome which may arise the concern of validity. There is a trend to subdivide analysis to include only the same test (e.g. UPSIT)(99). However, when we compared studies using different odor identification tests in different groups. The respective effect size was UPSIT=1.41, Sniffin' Sticks Test =0.43, SOIT =0.63, and BSIT =0.36 in Group B (18-50 year). The effect size ranged from moderate to large, we thought the result was consistent with the one when we combined different tests together in Group B (18-50 year). For Group C, the respective effect size was Sniffin' Sticks Test = -0.03, SOIT=0.56, UPSIT=2.20. But there were 7 studies using Sniffin' Sticks Test, only 1 study using UPSIT, and 2 studies using SOIT in Group C. All the studies in Group A (<18 year) were employing Sniffin' Sticks Test as the odor identification test, there was no diversification in this group. Based on these, we prudently conclude that the separation of different odor identification in different group will not change the overall results. And the explanation on how to integrating different studies together clarify this concern in some degree [100].

Conclusion

On the basis of the outcome of present meta-analysis and considering the limitations of this study, we conclude that a significant gender effect was observed only for younger adult individuals aged 18–50 years; no significant gender difference was found in individuals <18 or >50 years old. Among the multiple mechanisms that could contribute to this gender dimorphism in human olfaction, hormone levels, especially for those of estrogen, may play the most important role.

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Authorship contribution

XCW, CPZ, and CLZ designed the review protocol. XCW, CPZ, and XX conducted the search. XCW, CPZ, YY screened the articles on eligibility and extracted the data. XCW, CPZ analyzed the data. XCW, CPZ, and CLZ wrote the paper. XCW, CPZ contributed equally and are considered co–first authors. CLZ has primary responsibility for the final content. All authors have read and approved the final manuscript.

Conflict of interest

The authors declare that they have no competing interests.

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