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Research Article

Human Olfaction and Sexual Dimorphism: An Integrative Review of Anatomy, Neurobiology, Endocrinology and Psychological Behaviour

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Abstract: Background: Evolutionarily speaking, the sense of smell is the oldest sense and is densely linked to the limbic circuitry that regulates emotion, memory and social behavior. No single source has ever brought together the various aspects of the difference between the sexes in their olfactory structure and function and the novel ways in which smell relates to psychological wellbeing. **Objective:** The study objectives are to gather, critically evaluate and systematically review the different research areas related to sexual dimorphism of the human olfactory system: anatomical, neurobiological, endocrinological, anthropological and clinical; and to link those areas to psychological behavior. **Methods:** A narrative-integrative review conducted through PubMed, Scopus and Web of Science databases from last 15-20 years with classic studies where applicable, to support and strengthen the overall work of the review. The term Terminologia Anatomica is used everywhere and the findings are divided into established, conflicting and emerging or speculative categories. **Results:** On average, women perform better than men at the three tests of odour identification, discrimination and threshold sensitivity; effect sizes are small in size. Post mortem and imaging studies suggest that there is more of an excess of olfactory bulb neurons in females, while the results on bulb-volume remain mixed. Hormonal changes in the brain cause e.g. women to process the sense of smell differently during the menstrual cycle, pregnancy and menopause. Due to its weighty overlap with limbic areas that control mood, memory and social bonding, olfactory dysfunction is also seen in association with depression, anxiety, schizophrenia and neurodegenerative disease. The existence of classical human pheromones and a functional vomeronasal organ is weak; the existence of classical chemosensory communication via the main olfactory system (MHC-related cues) can be said to have stronger but still doubtful ground. **Conclusion:** The human sense of smell is a sexually dimorphic, hormone-sensitive, real-world and clinically relevant sense that plays a true role in emotional and social life and is clinically relevant as a biomarker of neuropsychiatric and neurodegenerative processes. The results are preliminary due to the small effect size, methodological variations among the studies and cultural differences, so results should be taken with a pinch of salt and larger studies and cross-cultural consistent studies are needed.

Keywords: Olfaction, Sexual Dimorphism, Olfactory Bulb, Human Pheromones, Olfactory Dysfunction, Limbic System

INTRODUCTION

In evolutionary history this is the most primitive of the human senses-the first to develop-and the one most directly involved in the Limbic Brain-the brain of emotion and addiction- and, in past history, the least studied in medicine [1]. Unlike other senses, the olfaction has the property of sending primary afferents directly to the amygdala, entorhinal cortex and the hippocampus, without passing through the thalamus [2,3] that helps explain why smells have so potent, involuntary emotional response and why memories evoked by odours are so vivid, as first described as the "Proust phenomenon" [4,5].

Throughout the last century and into the present, it was believed that human olfaction was a throwback, based on an incorrect thought from the nineteenth century, comparing the human nose to that of a dog's [6]. The reversal of interest in olfaction and cognition and social communication that was sparked by the likes of HeLa cells [9] and reinforced by the demonstration that the odour world is far richer than other mammals' [10] has been rejuvenated by modern psychophysical studies demonstrating that humans can discriminate an enormous number of odour mixtures, these still being though as significantly less sensitive than other mammals for many biologically relevant compounds [7]. The molecular era started with the discovery that the multigene family for certain odorant receptors won the Nobel Prize in 2002 and remains as the conceptual foundation of combinatorial processing of odours [9].

Since then the field has developed receptor genetics [10-12] and central processing [13] understandings and created standardised clinical tools, like the University of Pennsylvania Smell Identification Test and Sniffin' Sticks [14,15].

One of the more consistently replicated and least mechanistically understood findings in this area is the slight female advantage in identification, discrimination and threshold [16]; and sex differences in the cellular composition of the olfactory bulb and/or in the size of the bulb (less consistently replicated [17]). This relates to endocrinology, because performance changes throughout the menstrual cycle, in pregnancy and menopause owing to changes in gonadal steroids which effect ORNs and with psychological behaviour in general, as there are links between pathology of the olfactory bulb and piriform cortex and depressive phenotypes [18-22]. Despite this, human pheromones and an intact vomeronasal organ are still debatable [23,24] and few studies have distinguished between the biological differences between the sexes and gender differences that arise through social processes in relation to olfactory behaviour. This review is based on a careful combination of the anatomical, physiological, neurobiological, endocrinological, anthropological and clinical evidence regarding sexual dimorphism in human olfaction, while discarding conflicting evidence and speculations and focusing on Terminologia Anatomica in all cases.

Structural and Functional Basis of Human Olfaction

Anatomy of the Human Olfactory System: The peripheral olfactory apparatus begins in the olfactory region of the tunica mucosa nasi, on the concha nasalis superior and adjacent superior nasal septum, covering only a few square centimetres of nasal mucosa [25,26]. The epithelium is a pseudostratified neuroepithelium of bipolar receptor neurons, sustentacular support cells, regenerative basal stem cells and Bowman's glands, whose secretions form the mucus in which odorants dissolve [10]. Unmyelinated receptor-neuron axons bundle into fila olfactoria that cross the lamina cribrosa of the ethmoid bone to reach the bulbus olfactorius; this transcribriform route is a known site of weakness after trauma and has been proposed as a possible entry route for retrograde viral spread into the central nervous system, the "olfactory vector hypothesis" [27]. Inside the bulb, axons expressing the same receptor converge onto discrete glomeruli, synapsing onto mitral and tufted relay neurons and providing a spatial, "chemotopic" map of odour identity [28].

Mitral and tufted axons form the tractus olfactorius, reaching the piriform cortex, anterior olfactory nucleus, tuberculum olfactorium and amygdala without an obligatory thalamic synapse, a feature unique among human senses [29]. Secondary projections reach the entorhinal cortex and hippocampus, supporting episodic memory, while amygdalar projections underpin the coupling between smell and emotion and orbitofrontal projections support conscious identification and flavour perception; the insula adds disgust-related processing [30]. Together these structures form a continuous olfactory-limbic axis in which damage anywhere along the chain-epithelial injury, bulbar atrophy in Parkinson's disease, entorhinal tau pathology in Alzheimer's disease-can produce measurable dysfunction, making smell testing a low-cost window onto both nasal disease and central neurodegeneration [31].

Physiology of Olfactory Perception

They generally have low molecular weights, are volatile and are lipophilic, thus entering the tract through orthonasal or retronasal route, where they dissolve in the epithelial mucus and interact with the odorant receptors, a large multi-gene family in the mammalian genome that are G Protein-Coupled Receptors (GPCR). The activation of the olfactory (smell protein) G-protein Golf causes the creation of cAMP which opens cation channels, ultimately leading to depolarization of the neuron. In most cases each receptor neuron expresses one receptor gene and neurons containing the same receptor converge on the same glomeruli to represent a spatial map that is the basis for odor-object recognition. A multitude of specified receptor types is required for sensitivity to just a few hundred functional receptors to distinguish a very large number of different odours and odorant mixtures.

Lateral inhibition by periglomerular and granule cells increases the chances of detecting the differences among the activated glomeruli and centrifugal noradrenergic and cholinergic control tones the bulbar processing to attention and motivation. The piriform cortex represents an odour identity by a non-topographic coding in a distributed manner. This is reflected at all levels and over time high doses lead to very fast desensitisation - hence why recognized smells do not evoke much of a response, whereas new smells do. The ability to regenerate neurons throughout life, particularly the ability of the olfactory epithelium to regenerate, in which globose basal cells are the major source of generations, is also unusual to most neural tissues and is the basis of olfactory training as a therapy for recovering from various types of anosmia, such as post-traumatic and post-infectious anosmia.

Neurobiology of Olfaction

Olfactory processing is influenced at all stages by a variety of neurotransmitters. Because of the marked olfactory deficits observed in PD, dopaminergic periglomerular interneuron(s) that control the gain of the glomerulae and are involved in the processing of the odour reward are of particular interest. This is presumably via serotoninergic input from the raphe nuclei which is known to modulate olfactory sensitivity and has a well-documented relationship with depression.

The basal forebrain, including cholinergic projections, help to discriminate and learn, the GABAergic provide inhibitory tone, while the glutamatergic provide excitatory signalling onward.

Olfaction has a peculiar social character, with unique neuropeptides. Oxytocin and vasopressin are produced in the hypothalamus and exert their effects on receptors distributed throughout the olfactory and limbic areas (as well as the olfactory bulb and anterior olfactory nucleus) and that vasopressinergic neurons have been associated with conspecific recognition in animal models [32]. These neuropeptides have been found to guide social cognition, trust and stress reactivity in humans and although humans are more reliant on vision and hearing to communicate with each other, an olfactory route is equally germane to understanding these systems in Autism Spectrum Disorder (ASD) [33]. Under stress, the HPA axis may regulate the threshold and hedonic evaluation of the smell via GR in the bulb and amygdala (both suggested) providing a plausible mechanism for cortisol's effect on this ability under stress.

At the network level, olfactory information goes through at least four parallel circuits: A mesolimbic reward circuit for hedonic evaluation; an amygdala-insula circuit for affective tagging of odours; especially threatening odours; a hippocampal-entorhinal memory circuit giving the power to olfactory sensory stimuli to trigger autobiographical memory; and an orbitofrontal-prefrontal executive circuit involved in conscious identification and labelling of odours in words. The importance of each circuit seems to fluctuate from male to female and from premenstruum to postmenstruum, a fact which is best illustrated by the sexually dimorphic evidence to be discussed next.

Sexual Dimorphism and Its Biological Determinants

Sexual Dimorphism in Human Olfaction: Across all of identification, discrimination and detection threshold, the only consistent finding that has been replicated here is the small but highly-documented female advantage on these tasks observed through a large meta-analysis that included tens of thousands of people along the lifespan. This advantage is seen as early as in childhood, it lasts through adulthood and is found across cultures; although the size of the advantage remains moderate to small and is less noticeable in some studies after adjusting for age, smoking and cognitive performance.

Things aren't simple at the structural level. However, in one stereological postmortem study, women showed significantly higher number of mitral cells and the number of total bulb neurons although there was no volume difference, implicating a higher density of mitral neurons and total bulb neurons, but not necessarily larger size [17]. The volume of bulbs has been reported but results have been inconsistent which may be related to a variety of factors such as sample size, protocol and age of bulb. Functional imaging provides an associated yet also different image: Within a frequently quoted PET study androstadienone specifically activated the hypothalamus in women and not men, while estratetraenol did just the opposite; specifically, it activated the hypothalamus in men but not in women and this difference was taken as evidence for sex-specific central processing of these chemo signals [34].

There's plenty of documented modulation of hormones, but it's complicated. Experimentally, both hormones, the hormones in the menstrual cycle, suppress responses of the receptor-neuron in response to certain smell stimuli-this suggests a plausible peripheral mechanism for cyclical changes in sensitivity reported many years ago in women. There have been several studies that have found lower (i.e. more sensitive) detection thresholds in the periovulatory phase and reduced sensitivity during the menstruation phase, although not all studies find this so. During pregnancy, there is an increased sensitivity and a change of hedonic response, which is plausibly linked to increased oestrogen and progesterone, but is mainly based on self-report. Some reports from others have found little or no effects of menopause, while others found mild decreases, but these were confounded with normal aging.

There's been less direct research on the role of testosterone, though in some studies, women who had high levels of androgens were found to have a decreased sensitivity, again a female advantage. She has demonstrated that there is a functional polymorphism in the OR7D4 receptor that determines the perception of androstenone derivatives, indicating that the perception of such odours is an independent and heritable genotype and so shaped the perception of steroid-derived odours independently of it [11]. In both sexes, there is well-defined age-related decline and there seems to be a slightly larger decline in men, but with various complications from comorbid disease, smoking and cumulative exposures, simple comparisons are problematic.

Although a number of points are statistically sound, they are at the same time rather small in absolute size; the biological versus cultured sex differences in processes such as organisational and activational actions of hormones in relation to human olfactory circuitry are poorly disentangled compared to rodent studies; most studies failed to separate biologically-induced sex from socially-induced gender differences in exposure, in self-report and in smoking behaviour. This is a good reminder to read findings about sex differences with a grain of salt.

Endocrine Regulation of Olfactory Function

There is a periphery to cortex interaction between gonadal and adrenal steroids. This suggests a possible mechanism for cyclical sensitivity changes: oestrogen receptor expression is noted in the epithelium, the bulb and in downstream targets of the bulb in the "limbic" parts of the brain and experimental studies show that oestradiol decreases the

responses generated by odorant-evoked receptor-neurons. Progesterone functions in the same way acting through membrane progestin receptors and thus high hormone levels during the luteal phase and low hormone levels during the menstrual phase result in distinct, although not completely uniform, olfactory phenotypes. Testosterone effects in man are not as thoroughly documented but it is known that there are androgen receptors in the pertinent limbic areas and the altered sense of smell in hypo gonadal patients is suggestive.

Oxytocin and vasopressin contribute to this endocrine axis by attenuating responses in the amygdala/ventromediostriatal regions to social-relevant odours, with a region that partially overlaps with regions also involved in sex-differentiated processing of chemo signals. Under stress, cortisol affects the hedonic evaluation of olfactory stimuli via the glucocorticoid receptor in the bulb and blunted discrimination of neutral odours in some studies, reflecting attentional narrowing under stress and increased sensitivity to threat-odour via the glucocorticoid receptor in the amygdala. Thyroid hormones are less extensively investigated here and play an important role in neurodevelopment and myelination; hypothyroidism has been correlated to hyposmia which improve with the treatment with thyroid hormones, thus indicating a permissive rather than a modulatory action. Together, these results demonstrate that olfactory function is not static, but rather is dynamically regulated throughout the reproductive life span and that this has implications for understanding and explaining the notion of sex differences without considering cycle phase, contraceptive use, pregnancy or menopausal status.

The gene repertoire of human ORs shows a low ratio of functional to pseudogenes relative to rodents or prosimian primates, consistent with a hypothesis that loss of one function (olfactory) went hand-in-hand with the evolution of full trichromatic colour vision in catarrhine primates and, separately, howler monkeys [35]. Besides this "sensory trade-off" hypothesis is not resolved, with a subsequent comparative genomic study contesting the large inter-species difference between human and other great apes in the pseudogene ratio as originally suggested. Despite not having as many receptor genes as some mammals, humans have a coding system in the form of a logical combination of these genes that is sufficient to code for a vast number of odorants.

Olfactory cues are believed to have aided in certain problem solving tasks which were important to reproductive fitness-these include judging the familiarity of kin, avoiding unfamiliar foods or domesticates, determining the genetic compatibility of Partners-consistent with other accounts of mate preference that emphasize different reproductive costs that have been experienced by males and females throughout time [36]. Differences in selective pressures between the different species and groups are evident in the intact receptor repertoire and the more or less developed vomeronasal system, particularly those of catarrhines primates (apes, monkeys and apes) depend much more on systems based on vision and hearing than those that rely on chemosensory scavenging, which are reflected by a vestigial or functionally nonexistent vomeronasal organ and a smaller receptor repertoire.

Basic physiological facts about the human sense of smell are universal, but odour vocabulary, hedonic norms and activities like the use of perfumes and rituals are diverse and much different from one culture to another, so that cross-cultural comparisons must take these differences into account, as naive comparisons of "innate" ability are at risk of being confounded by linguistic resources and habituation. This variability provides good ground for caution and uncertainty of generalization on un-qualified samples (Figure 1).

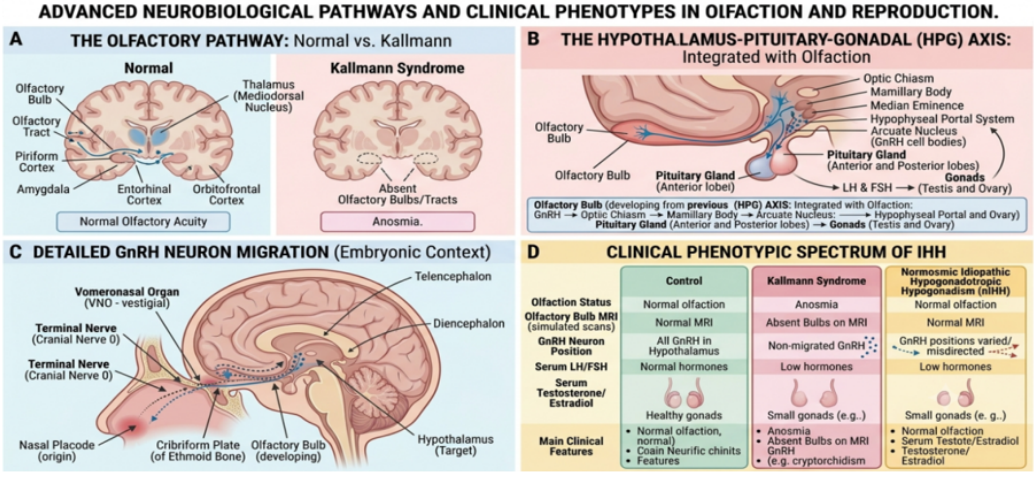

Figure 1: Advanced Neurobiological Pathways and Clinical Phenotypes in Olfaction and Reproduction

Behavioural, Clinical and Future Perspectives

Olfaction and Psychological Behaviour: Because olfactory afferents reach limbic structures without a thalamic relay, olfaction sits in an unusually direct position to shape emotion and motivated behaviour and a substantial literature documents two-way links between olfactory function and psychiatric symptoms. In rodents, olfactory bulbectomy produces a behavioural syndrome-hyperactivity, anhedonia-like deficits, impaired habituation-that responds to chronic but not acute antidepressant treatment, a time course mirroring clinical antidepressant efficacy and long used as a depression model, though debate continues over its construct validity given the surgery's non-specific effects on nearby limbic tissue [37]. In humans, reduced odour identification and, in some studies, smaller bulb volume accompany depressive states, with partial recovery after successful treatment; bulb volume also tracks inversely with symptom severity and early-life adversity.

Olfactory dysfunction is similarly tied to anxiety and lower subjective wellbeing, with self-rated olfactory function correlating with quality of life independently of objective performance-smell loss appears to carry a psychological cost of its own. Odour-evoked memories tend to be unusually vivid and emotionally charged, a property attributed to the direct link between piriform cortex, entorhinal cortex, hippocampus and amygdala and one that has drawn therapeutic interest in olfactory cueing for post-traumatic stress disorder.

On reward and decision-making, pleasant odours boost approach behaviour and favourable ratings of unrelated stimuli, consistent with mesolimbic dopaminergic engagement, while aversive odours increase risk aversion and social avoidance [36]. Olfactory performance correlates modestly with general cognitive performance in some studies, likely reflecting shared frontal-executive and hippocampal dependence rather than a direct causal link. A smaller, emerging literature connects olfactory function to sleep quality, though this remains far less studied than the mood and memory literature. Together, this evidence supports olfactory circuitry as a sensitive, non-specific gauge of limbic and prefrontal integrity.

Olfaction and Human Social Behaviour

From birth point on olfactory information influences social communication in humans. Mothers are able to locate their own infants by smell by the end of the first week and infants prefer to be lured by their maternal body odours, suggesting a pre-existing two way bonding system related to smell and attachment and bonding with mother and infant that is formed within the first few days of life [37,38]. There is evidence of chemosensory learning in utero, with foetuses being able to learn olfactory information before they are born and this aspect may influence earlier food preferences and maternal recognition [38].

In mate choice, human body smell seems to contain information about genetic dissimilarity through major histocompatibility complex (MHC or HLA in human)-several but not all studies conclude that MHC-dissimilar male body odours appear to be the more pleasant, effect hypothesized to be advantageous due to heterozygosity of offspring [39,40]. Body odours with added MHC peptide ligands (derived from their own body) evoke a distinct right (Right-Middle-Frontal) cortex region (RFM) that people can tell or rate as more familiar [41]. However, more extensive meta-analyses of both genetic and relationship data have not been statistically significant and have pointed out obvious publication bias - where it exists, the true mate preferences seem to be quite small and fail to be consistently replicated [42,43].

Body odour symmetry also relates to independent judgements of attractiveness of the body and the visual and olfactory information seem to be processed together when judging attractiveness of a partner-though it remains unknown how important this is in the wild [44]. The shape and proportions of the external nose itself do not only trigger its olfatory connection; also from an anatomical perspective, the ability to perceive the external nose as beautiful is influenced by neither homologies nor only by the nose itself [45]. Emotions of the donor in addition to the choice of her mate also affect the physiology and behavior of the recipient through inner communication via body odor; and chemosignals from emotionally aroused donors influence those of the recipient, not just in ways that are known as pheromones but in other olfactory ways, "olfactory emotional contagion".

The chemical nature of stimuli complete with producing fixed and hard-wired responses that are independent of learning, or called "true human pheromones," are controversial and should be conceptually distinct from chemosensory communication per se. Although there is evidence that a Vomeronasal Organ (VNO) is physically present in many adults, a VMO is not actually equipped for transduction through the central connections or the presence of neuroepithelium, suggesting that it is at best vestigial [46-48]. Experimentally blocking the VNO does not negatively affect responding to candidate pheromones, like androstadienone, implying that real human chemosignalling occurs through the main olfactory system, not via an accessory route through the VNO. Most reviewers thus prefer the less emotive word "chemosignal" to the word "pheromone" when it comes to human communication.

Clinical Relevance

Olfactory dysfunction is an important early, clinical feature in many neurologic, psychiatric and otorhinolaryngological diseases. After the onset of the COVID-19 pandemic, abrupt onset anosmia, which is frequently reported without nasal congestion, was identified as a very early diagnostic screen associate with the disease and incorporated into the

diagnostic screening process; in a subset of patients, anosmia was reported to last for months after the onset of the disease [49]. In Parkinson's it is observed in the majority of patients, is more commonly a marker of prodromal disease and typically occurs years before motor symptoms and is now regarded as an early marker of Lewy body disease in the olfactory bulb. Our understanding of Alzheimer's pathogenesis associates identification dysfunction with amyloid and tau accumulation [50,51] as well as with the transition from MCI to dementia, suggesting that foreboding entorhinal participation. Impairment also has been observed, but not in every case, in frontotemporal dementia.

The under-recognition of smudges is not only a feature of schizophrenia, but is also seen in a lesser degree in unaffected 1st-degree relatives and those at clinic high risk for schizophrenia, thus adding odor recognition a likely vulnerability marker [52]. Along with depression and anxiety there is some loss of sensitivity and identification and in some research, decreased bulb size - some recovery following treatment. Initial findings of ASD suggest that there is an atypical smell processing ability both in social judgement of smelling and the extent of the abnormality is inconsistent across studies [53]. Alterations in taste and smell sensitivity during the course of eating disorders have been reported in anorexia nervosa and bulimia nervosa and were partially recovered when there were clinical improvements, indicating that the taste and smell sensitivity are associated with the chronicity of the illness and may not be a stable trait marker [54].

Often the olfactory axons across the cribriform plate are damaged, or there is post-traumatic direct damage to orbitofrontal and temporal olfactory cortices, resulting in clinically relevant and common post-traumatic anosmia that is related to the severity of the injury [55]. Chronic rhinosinusitis, occurring in a high proportion of patients, is a very common cause of conductive dysfunction that leads to an inability to perceive smell (olfactory loss), as well as, in more advanced disease, direct damage to the neuroepithelium and is one of the more common reversible causes of significant olfactory loss, with other anatomical variants (septal deviation, concha bullosa) being recognised epidemiologic factors [56,57]. In all of these circumstances, standardised psychophysical testing is a low cost, non-invasive test that can be used as an aid to clinical evaluation, particularly as this progresses over time.

Current Controversies and Future Directions

Current Controversies: Several parts of this literature remain genuinely unsettled. Whether true human pheromones exist in the strict ethological sense is still unproven; claims about specific molecules such as androstadienone and estratetraenol rest on a relatively small number of studies and the vomeronasal organ looks functionally vestigial, undermining pheromone hypotheses modelled on rodent signalling.

Reproducibility is a broader worry across this literature. Several influential early findings, including menstrual synchrony driven by axillary chemosignals, have not held up under scrutiny; critical reanalyses have found substantial statistical flaws in the original work and more recent studies have failed to find compelling evidence for ovulatory-cycle shifts in body-odour attractiveness, contradicting earlier reports [58,59]. Sample sizes across much of the dimorphism and MHC-preference literature remain modest by current standards and publication bias favouring positive findings has been explicitly documented.

Cultural influences on olfactory hedonics and vocabulary are substantial and often under-controlled in cross-national studies, risking conflation of biological and learned differences. A related issue is sex versus gender: most studies operationalise "sex" through binary self-report without genetic or endocrine confirmation and gendered behaviours such as fragrance use and smoking can confound biologically driven differences. Methodological heterogeneity-different test batteries, odorant sets and definitions of anosmia versus hyposmia-further complicates cross-study comparison and meta-analytic synthesis.

Future Directions

Future developments in precision microstructural imaging of the OB and related cortical regions may provide a more reliable and individualised measure of integrity of the OL network that is more sensitive to changes in the brain than a psychophysical test, particularly in combination with longitudinal designs which can isolate sex differences from hormone level fluctuations and/or other state-dependent factors. In the future, stratifications based on chemosensitivity might be possible using personalised approaches based on olfactory phenotyping and genetic resources such as the receptor polymorphisms (e.g. for neurodegenerative diseases), which could be used to screen for early neurodegenerative disease and then provide personalised olfactory rehabilitation.

The combination of large, multimodal datasets with machine-learning analysis could facilitate addressing the reproducibility issues by providing adequately powered (and pre-registered) studies in a variety of populations; electronic-nose and other chemical-analytic data tools can be used in clinical or forensic studies in tandem with human psychophysical testing. Neurogenetic works, such as single cell transcriptomic analyses of epithelium and bulb could foster a more focused understanding of basal stem cell contribution to neurogenesis and regeneration, which has direct connection to diseases of post-viral, post-traumatic and neurodegenerative rehabilitation. Multi-omics integration, the integration of genomic, hormonal, microbiomic and neuroimaging data, seems to be one of the most promising avenues

for understanding the mechanistic basis of sexual dimorphism, the trait likely being polygenetic and multifactorial. As for clinical use, prospective, cross-cultural research with well-standardized and validated batteries of instruments that specifically document menstrual cycle phase, type of contraceptive currently in use and pregnancy status as well as regular reporting of effect sizes and not just levels of statistical significance are needed.

CONCLUSION

In this review we have collected together existing, anatomical, physiological, neurobiological, endocrinological, anthropological and clinical evidence from the literature regarding sexual dimorphism of human olfaction and its relationship to psychological behaviour. The olfactory epithelium and olfactory bulb on the nose and their direct projections to the regions of the Limbic system, have in shape, a close association to emotion and memory. The modest but factually existing female advantage throughout life could at least in part be explained by the actions of neurotransmitters, neuropeptides and steroid hormones on olfactory processing on all levels. Olfactory function is also closely linked to psychological and clinical function, such as mood, memory, social cognition and reward and is therefore a sensitive, non-specific marker in psychiatric and neurodegenerative diseases.

There are really significant gaps: Although mechanisms underlying the difference in size of the olfactory bulbs have been deciphered, true human pheromones and pheromone-producing vomeronasal organs have yet to be proven; and a significant proportion of the field continues to study moderately sized, culturally limited samples. Precision neuroimaging, precision neurogenetics, precision endocrinology and cross-cultural sampling are all necessary to develop a more precise, clinically useful model of the role of olfaction in psychological life, though particularly multi-omics and longitudinal frameworks will be needed to move beyond the documentation of sexual dimorphism. In the meantime, both clinical and research practitioners must be cautious with the conclusions drawn from existing evidence; do not accept everything or overlook conflicting data; and not jump to speculations.

Conflict of Interest

The authors declare that there are no conflicts of interest to disclose in relation to the publication of this manuscript.

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Ethical Statement

The author's state that ethical approval was not required for this study because it is a review-based work. However, all data sources used in the study have been carefully acknowledged and properly cited in accordance with accepted academic and scholarly standards.

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