Review Article

Current status and significance of research on sex differences in neuroscience: a narrative review and bibliometric analysis

Running title: Sex differences in neuroscience research

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Abstract

This review aims to highlight the importance of research on structural, functional, molecular-biological, and disease-specific sex differences in the brain, and to examine current bibliometric indicators related to research on sex differences. The Web of Science Core Collection was searched for related articles from 2010 to 2023. Structural and functional brain differences according to sex, including variations in communication patterns between hemispheres, may play a role in mental disorders. Sex differences in

neurotransmitters such as serotonin, dopamine, and GABA contribute to disparities in mental health, addiction, and neurodevelopmental conditions. Neurodevelopmental disorders such as autism spectrum disorder (ASD) and schizophrenia exhibit sex-based differences in prevalence, symptoms, brain changes, and neurotransmitter disruptions under hormonal influence. There is a growing body of research on depression, adolescence, the hippocampus, the amygdala, and cognition, highlighting the importance of considering sex/gender factors. Recent studies on sex differences in brain diseases have identified variations in brain structure, function, and neurophysiological substances, as well as in hormones and genes between the sexes. The incidence of psychiatric disorders such as ASD, depression, anxiety, and Alzheimer's disease is increasingly being linked to sex differences, and the need for research into the mechanisms underlying these differences is gaining recognition. However, there remains a significant gap in sex-specific neuroscience research related to the diagnosis, treatment, prevention, and management of these conditions. Advancing inclusive research will require comprehensive training, a consensus on methodology, diverse perspectives through collaborative frameworks, governmental/institutional support, and dedicated funding to create suitable research environments and implementation strategies.

Keyword: Alzheimer disease; Brain, Brain diseases; Mental health; Psychiatry; Sex characteristics

Introduction

Background

The latest Global Burden of Disease (GBD) report [1] indicates that the worldwide need for diagnosing and treating mental disorders has surged significantly in recent years. This category includes depressive disorders, anxiety disorders, bipolar disorder, schizophrenia, autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and neurodegenerative brain disorders. Notably, substantial sex differences have been observed in the prevalence of depression, anxiety disorders, ASD, and neurodegenerative brain disorders [2-6] (Figure 1).

Depressive disorders, characterized by changes in mood, interest, energy, sleep, and appetite, occur more than twice as often in women as in men. ASD, a significant brain development disorder marked by

difficulties in social communication and interaction, along with repetitive behavior patterns or interests, is approximately four times more prevalent in men than in women [5, 7, 8]. Alzheimer's disease (AD), a common condition of aging where the brain gradually loses function and disrupts daily living, occurs twice as frequently in women as in men [9-11]. Parkinson's disease (PD), a movement disorder that impairs the ability to control movement, has been reported to be more than twice as common in men as in women [12-14]. Sex differences have been observed in several psychiatric disorders, but the causes of these differences remain largely unknown [4, 15, 16]. Several factors are thought to be involved, including genetic, biological, and environmental factors, but more research is needed to elucidate these influences.

Sex differences in the incidence of mental disorders serve as both direct and indirect indicators that biological or social factors may predispose different sexes to various brain diseases. This recognition has spurred a growing interest in researching the causes behind these sex differences in mental disorders [1, 4, 17, 18]. For mental disorders with evident sex differences, it is advisable to design and conduct studies specifically aimed at identifying the underlying causes of these disparities. By analyzing the sex/gender-specific characteristics of brain diseases and uncovering the mechanisms behind sex differences, researchers can develop more effective and safer diagnostic and treatment strategies, as well as preventive and rehabilitative measures to enhance mental health.

To date, several biological factors—including variations in brain structure and function, influences of neurotransmitters and hormones, and genetics—as well as sociocultural factors, such as individual experiences and learning, have been suggested as potential explanations for sex differences in mental disorders [19, 20]. In light of these factors, research into sex differences in the brain seeks to uncover the physiological and structural distinctions between male and female brains [21]. The field of research on sex differences in the brain is growing, driven by advances in various technologies such as brain imaging, genetic analysis, neural network studies, big data, and artificial intelligence.

Objectives

This review highlights the importance of research into sex differences in neuroscience. It specifically updates the following areas: structural and functional sex differences in the brain, sex differences in

neurotransmitters, sex differences in mental disorders, and bibliometric findings related to sex differences in neuroscience research.

Methods

Ethics statement

This study does not involve human subjects; therefore, neither institutional review board approval nor informed consent was required.

Study design

This study was a narrative review and bibliometric study based on a literature database search.

Literature search/information source and search strategy

The Web of Science Core Collection (Clarivate) was searched for the bibliometric analysis. The authors reviewed the presence of sex/gender-specific keywords in the titles and abstracts of articles and reviews within the field of biological sciences, published from 2010 to 2023. The search utilized the keywords ["sex factor*" OR "sex characteristic*" OR "sex difference*" OR "gender factor*" OR "gender characteristic*" OR "gender difference*"] NOT ["sex* partner*" OR "sex* selection*" OR "sex* behavior*" OR "sex* behavior*"]. More specific search terms are included in Supplement 1. Additionally, to identify the main keywords and major research areas related to sex differences in neuroscience and psychiatry, we analyzed the keyword network using Vos Viewer (https://www.vosviewer.com/).

The associations between article titles and keywords, identified using sex/gender-specific search terms through Vos Viewer, revealed that research primarily focused on three main topics: brain structure and function (fMRI, amygdala, hippocampus, etc.), mental disorders (depression, anxiety, schizophrenia, etc.), and neurotransmitters (dopamine, etc.). The existing literature on these topics, with an emphasis on sex/gender differences, was thoroughly identified and reviewed.

Results

A total of 5,491 articles were identified that discussed structural and functional sex differences in the brain; 4,227 articles addressed sex differences in neurotransmitters, and 14,401 articles explored sex differences in mental disorders

Structural and functional sex differences in the brain

Recent meta-analyses [18, 22] have demonstrated structural sex differences in various brain regions. These differences include the amygdala, hippocampus, temporal lobe, and insular regions, with men generally having a larger overall brain volume than women. Specific areas such as the left frontal gyrus, left occipital gyrus, left insula, right frontal orbital gyrus, and left occipital sulcus also showed differences. Additionally, variations in white matter regions were observed in the following sequence: midbrain, corpus callosum, right anterior cingulate gyrus, right superior colliculus, and left medial anterior cingulate gyrus [22]. Furthermore, a study on the diffusion-based structural connectome of the brain [23] confirmed that men's brains exhibit more intra-hemispheric communication, whereas women's brains show more inter-hemispheric communication. This study also indicated that brain development in men and women diverges from an early age, leading to structural and functional brain differences in adolescence and adulthood. These structural and functional changes may influence the development of neuropsychiatric disorders, particularly during adolescence—a period when physiological and behavioral differences between the sexes become more pronounced, and the risk of developing neuropsychiatric disorders increases [24]. Notably, activity in the left amygdala significantly increases in women during adolescence, which is partly associated with heightened anxiety.

Although numerous studies have analyzed the structure and function of the brain, significant gaps remain in our understanding of the behavioral and physiological differences between men and women, as well as the specific variations in brain structure and function related to mental disorders. Further research into brain structure, function, and sex-specific symptoms is essential to enhance the diagnosis and treatment of the growing prevalence of mental disorders worldwide.

Sex differences in neurotransmitters

Sex differences have also been reported in neurotransmitters that play a crucial role in regulating brain function, such as serotonin, dopamine, and γ-aminobutyric acid (GABA). Serotonin, a neurotransmitter involved in mood regulation, including depression and anxiety disorders [3, 25-28], exhibits sex differences in its expression, role, and receptor [25]. Women have higher levels of serotonin in their blood compared to men [18], and these elevated serotonin levels have been linked to higher levels of estrogen, a sex hormone associated with female reproductive organs [27]. Additionally, women show significantly higher expression of 5-HT1A receptors in various cortical and subcortical brain regions than men [25]. However, the rate of serotonin synthesis is 52% faster in men than in women [26]. This sex difference in serotonin has been proposed as a potential cause for the varying incidence of depression, anxiety disorders, and bipolar disorder between sexes, suggesting that sex-specific treatments and prevention methods warrant further investigation [28].

Sex differences also exist in dopamine, which plays a crucial role in regulating the motor and reward systems [29, 30]. Notably, female hormones such as β-estradiol have been shown to enhance the activity of dopamine cells, resulting in increased dopamine release [15]. Additionally, several physiological sex differences have been identified, including variations in the neuroanatomical distribution of dopamine neurons, basal dopamine levels, and the influence of ovarian hormones [30]. Sex differences in dopamine have been suggested to contribute to sex differences in addiction [29, 31] and PD [12, 18, 29], but more detailed research on disease-, brain region-, and behavior-specific mechanisms is needed.

GABA, an inhibitory neurotransmitter that acts as an excitatory neurotransmitter in the developing brain, is regulated by sex hormones, particularly estrogen, during the perinatal period of sensitivity. Researchers have observed sex differences in the volume of certain nuclei and in the frequency and type of synapses in areas such as the hypothalamus, hippocampus, and preoptic area [32]. Additionally, estrogen has been shown to modulate GABA receptors, controlling their synaptic inhibitory efficacy and leading to differences in signal transduction between the sexes [33]. These findings have led to the hypothesis that sex differences may contribute to conditions such as ASD, ADHD, and epilepsy that develop during this critical period [32, 34, 35]. However, further research is necessary to fully understand the underlying mechanisms and potential treatments.

Sex differences in mental disorders

Brain developmental disorders

ASD, the most common brain developmental disorder, affects approximately 1 in 36 children; boys are four times more likely to be affected than girls, and their symptoms tend to differ [7]. In a study involving over 2,400 individuals with ASD aged 4-18 years [5], it was found that females with ASD generally exhibited greater impairments in social communication skills, overall IQ, and adaptive functioning. In contrast, males with ASD displayed more prevalent restricted and repetitive behaviors (RRBs). Additionally, males with ASD had larger than normal volumes of grey matter, white matter, and the hippocampus, whereas females with ASD showed smaller volumes in the right hippocampus compared to typical levels [8]. Sex hormones, particularly estrogen, have been demonstrated to influence brain development by affecting the synthesis and receptor expression of GABA, an inhibitory neurotransmitter [7]. Estrogen has also been shown to increase levels of glutamate, a brain-active neurotransmitter, which affects receptor signaling and enhances NMDA receptor expression [34]. Moreover, progesterone can inhibit glutamatergic responses and exhibits sexual dimorphism in certain brain regions. Lower plasma glutamate levels have been observed in individuals with ASD [36].

Schizophrenia is classified as a brain developmental disorder. Research has shown that men are more likely to exhibit positive symptoms such as delusions, hallucinations, and aggression, whereas women tend to develop negative symptoms like depression, anxiety, and social isolation [37]. The typical age of onset varies by sex, occurring between 15 to 25 years in men and 25 to 35 years in women, with another peak occurring after menopause. Changes in brain structure and function are also evident; in men, the prefrontal lobe decreases in size and becomes more asymmetrical than normal, whereas in women, the prefrontal lobe increases in size and shows enhanced white matter connectivity. Furthermore, neurotransmitter activity differs between the sexes, with an overactivity of dopamine in males and glutamate in females [29, 37].

Mood disorders

Depressive disorders, including post-traumatic stress disorder, generalized anxiety disorder, and major

depressive disorder, are more common in women than in men [1, 3, 28, 38]. Brain imaging analyses of male and female patients with depressive disorders [38] have revealed changes in the size of the hippocampus, amygdala, habenula, anterior cingulate cortex, and corpus callosum. These analyses also showed altered function in the frontal and temporal gyri, caudate nucleus, and prefrontal cortex, as well as microstructural changes in the corpus callosum and its prefrontal projections. Additionally, sex differences in brain circuitry and related systems have been identified [3]. When examining the circuits activated by a stimulus that leads to a behavioral or physiological response, comparisons between the sexes may reveal that the same circuits are involved, but the response may be more intense or prolonged in one sex compared to the other. For instance, corticotropin-releasing factor activates the arousal system more significantly in women than in men. Alternatively, it may be activated only in one sex; for example, flight stress activates anterior limbic projections to the dorsal thalamus, mediating stress in men but not in women, and sometimes results in completely different behaviors in men and women. For instance, oxytocin activation of oxytocin receptor-containing interneurons in the medial prefrontal cortex induces anxiety in men and altruistic behavior in women. In some cases, the physiological and/or behavioral effects may be the same in both sexes, but there are sex differences in the circuits and mechanisms that produce these effects. For example, when recalling emotional content, the right amygdala is activated in men, whereas the left amygdala is activated in women. While sex differences have been observed in various brain regions and systems associated with depressive disorders, we have yet to identify sex-specific etiologies and mechanisms for treatment, management, and prevention. More focused research on sex differences is essential to unravel the complexities of brain circuitry, hormonal influences, and physiological and behavioral differences.

Neurodegenerative disorders

Neurodegenerative disorders are characterized by the loss of neurons, typically associated with aging. AD, a major neurodegenerative disorder, disproportionately affects women, with incidence rates more than twice those in men. Conversely, PD predominantly affects men, with rates more than twice as high as those in women.

AD, one of the most common neurodegenerative disorders, is a progressive condition that begins with

mild memory loss and can progress to a complete inability to interact with others or respond to the environment. This progression occurs as the brain regions responsible for thinking, memory, and language become impaired. Women with AD experience a faster cognitive decline than men, and studies have shown that brain atrophy also occurs more rapidly in women [9, 39]. Furthermore, depression, sleep disorders, and stress are risk factors for developing AD. Notably, depression, which is more commonly diagnosed in women, increases the risk of AD. Sleep disorders, which tend to worsen during menopause, contribute to the accumulation of amyloid beta, a protein implicated in AD. Estrogen also plays a significant role in AD. It regulates synaptic plasticity and enhances neural survival. However, the rapid fluctuations in estrogen levels after menopause are linked to an increased risk of brain damage [11].

PD is the second most common neurodegenerative disease after AD and is characterized by severe movement disorders such as bradykinesia, rigidity, tremor, and gait disturbances, which are caused by the loss of midbrain dopaminergic neurons [40]. The incidence of PD is higher in men than in women; however, women experience higher mortality rates and faster disease progression. Additionally, motor and rapid eye movement sleep behavior disorder symptoms are more prevalent in men, and studies have shown that the cortex is thinner in men than in women in the central and pre-central regions. Moreover, men exhibit greater total cortical and subcortical atrophy, and the volumes of the thalamus, caudate, insula, globular bodies, hippocampus, and brainstem are smaller in men [14]. A recent study revealed that cortical thickness varies between male and female patients with PD, influenced by age and disease duration [13]. Specifically, in men with PD, cortical thinning in six frontal lobes (bilateral caudal middle frontal gyrus, bilateral superior frontal gyrus, left frontal gyrus, and right orbitofrontal gyrus), three parietal lobes (bilateral inferior parietal gyrus and left superior parietal gyrus), and one limbic system region (right posterior cingulate gyrus) was associated with longer disease duration and older age. In contrast, in women with PD, only limbic regions showed an association with disease duration.

Bibliometric analysis of sex differences in neuroscience research papers and related keywords

A total of 57,628 articles are included in this bibliometric analysis. As research continues to uncover sex differences in brain structure, function, and neurotransmitters in various brain disorders, the

importance of sex/gender-specific research is becoming increasingly recognized. Specifically, understanding the sex-specific mechanisms involved in anxiety, depression, ASD, AD, and PD is crucial for the prevention and treatment of mental disorders and for protecting sex/gender-specific mental health.

Major scientific journals such as *Nature* [41, 42], *The Lancet* [43, 44] and *Cell* [45] have recognized the importance of integrating sex and gender considerations into research and are actively promoting and disseminating this approach. Concurrently, there has been an increase in the publication of sex/gender-specific research articles. Our search indicated a general rise in these publications (Fig. 2), with neuroscience and psychiatry experiencing a significant uptick since 2018. In contrast, cell biology and biology have shown minimal changes. This trend underscores the widespread sex differences observed in research findings within neuroscience and psychiatry, highlighting the critical need for sex/gender-specific research in these disciplines.

It was found that the keywords related to sex differences were most commonly associated with depression, anxiety, adolescence, and stress, and are connected through brain diseases, functions, and research methods (Fig. 3). Specifically, the brain regions of the hippocampus and amygdala were identified as having strong associations with sex/gender-related keywords. Additionally, topics such as age, stress, estrogen, and cognition were found to be closely linked with studies on sex/gender differences.

Discussion

Interpretation and suggestion

In this comprehensive review, we have substantiated the existence of both structural and functional disparities between sexes in the brain, while also elucidating the underlying mechanisms that contribute to sex/gender-specific differences in various disease states. The complex orchestration of perceptual,

learning, emotional, cognitive, and behavioral functions across all brain regions highlights the complexity of brain function. Consequently, the identification of sex differences in individual brain regions, along with multifaceted influencing factors, emphasizes the presence of sex/gender-specific differentials in overall brain function.

However, most existing brain research, particularly in animals, has focused on males. This has resulted in a body of knowledge that is biased and lacks consideration of sex-specific differences. A deficiency in sex/gender-specific research can lead to drug side effects and inefficiencies that vary between sexes/genders. Moreover, generalizing findings can result in the absence of tailored treatments and discrimination, as well as broader health issues due to insufficient knowledge.

Recent research into the fundamental causes of sex differences in brain disorders highlights a growing consensus that sex/gender-specific vulnerabilities and resilience to diseases might originate from the brain's sexual dimorphism. This view is supported by evidence indicating that biological differences, such as hormonal and genetic variations, affect brain structure, function, and neurotransmitter systems during development.

The findings from non-clinical studies on microglia published in 2018 were particularly revealing, as they highlighted sex-dependent disparities in gene transcription, protein synthesis, and cellular function and activity [49, 50]. Microglia, small cells in the central nervous system, play a crucial role in managing immune and inflammatory responses and are essential for neuron survival and the formation of neural circuits [51]. Initially observed in the early 2000s in response to estrogen, the detailed differences in microglial function between sexes were only thoroughly described in 2018. For example, it was discovered that female brains typically exhibit weaker inflammatory responses, which may provide increased resistance to certain diseases, while male brains may suffer exacerbated brain damage due to stronger inflammatory reactions [50]. Additionally, male microglia appear to be more reactive and mobile and exhibit a heightened expression of certain proteins compared to their female counterparts, which demonstrate a higher capacity for phagocytosis and gene expression related to cell repair and inflammation management [52]. These functional disparities could potentially explain the varied susceptibility to diseases between sexes, underscoring the need for further research to fully understand

how microglial sexual dimorphism contributes to these differences [53].

The importance of understanding biological sex differences in the brain is paramount. These differences are essential for enhancing the effectiveness and personalization of prevention, management, and treatment strategies for sex-specific conditions. Additionally, they provide insights into the intricate interplay of biological, environmental, and developmental factors that influence human behavior and identity. This knowledge also supports ethical and social debates, fostering inclusion and understanding across various sectors of society. Consequently, global neuroscience research initiatives are increasingly concentrating on exploring these mechanisms through the lens of sex differences. Notably, the Women's Brain Project [39, 54] serves as a key platform for advocating and disseminating research focused on understanding the numerous factors that affect women's brain health and the pathophysiological mechanisms of mental disorders that are commonly observed in women. This initiative is crucial in addressing the male bias in brain health research and aims to advance precision medicine by establishing a solid foundation of knowledge on sex/gender-specific brain functions.

The author suggests that research on neuroscience and psychiatric disorders should incorporate sex-specific considerations, particularly when studying conditions such as depression, anxiety, stress, adolescence, schizophrenia, and the hippocampus.

Conclusion

The predominance of single-sex studies in research has introduced biases, and a general lack of sex/gender-aware studies has hindered the expansion of informed clinical trials. These trials, which are essential for verifying the safety and efficacy of treatments, must incorporate sex/gender considerations in their designs and outcomes. The advancement of sex/gender-inclusive research relies on comprehensive training in these concepts, agreement on methodologies, and the integration of diverse perspectives through collaborative frameworks. Additionally, governmental and institutional support, coupled with appropriate funding, is crucial for enhancing research environments and ensuring the

thorough implementation of inclusive research strategies.

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Authors' contributions

All work was done by Heajin Kim.

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Data availability

Not applicable.

Acknowledgments

Not applicable.

Supplementary materials

Supplement 1. Search terms used in this study.

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Figure legends

Fig. 1. Several neurological disorders that exhibit sex differences. Male bias (Grey), Female bias (Yellow)

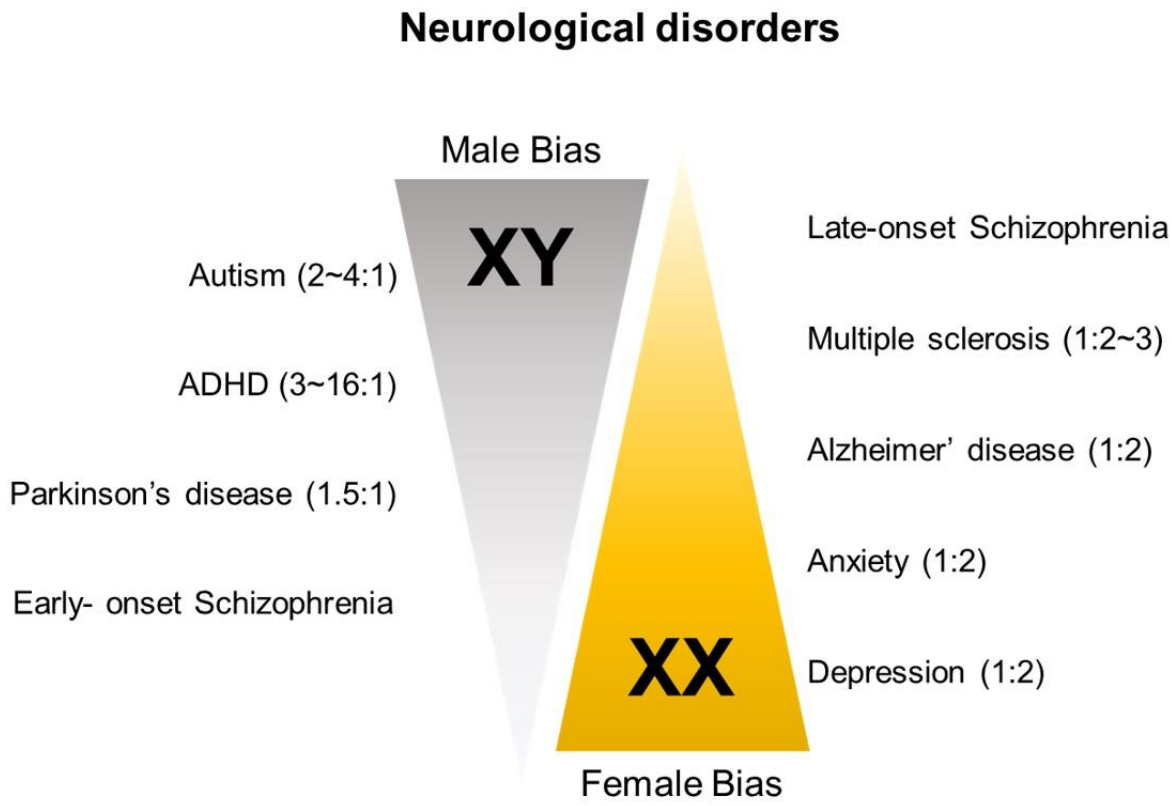

Fig. 2. Trends in sex/gender-specific papers (number of publications) in neuroscience (red), psychiatry (pink), behavioral sciences (green), cell biology (blue), and biology (purple)

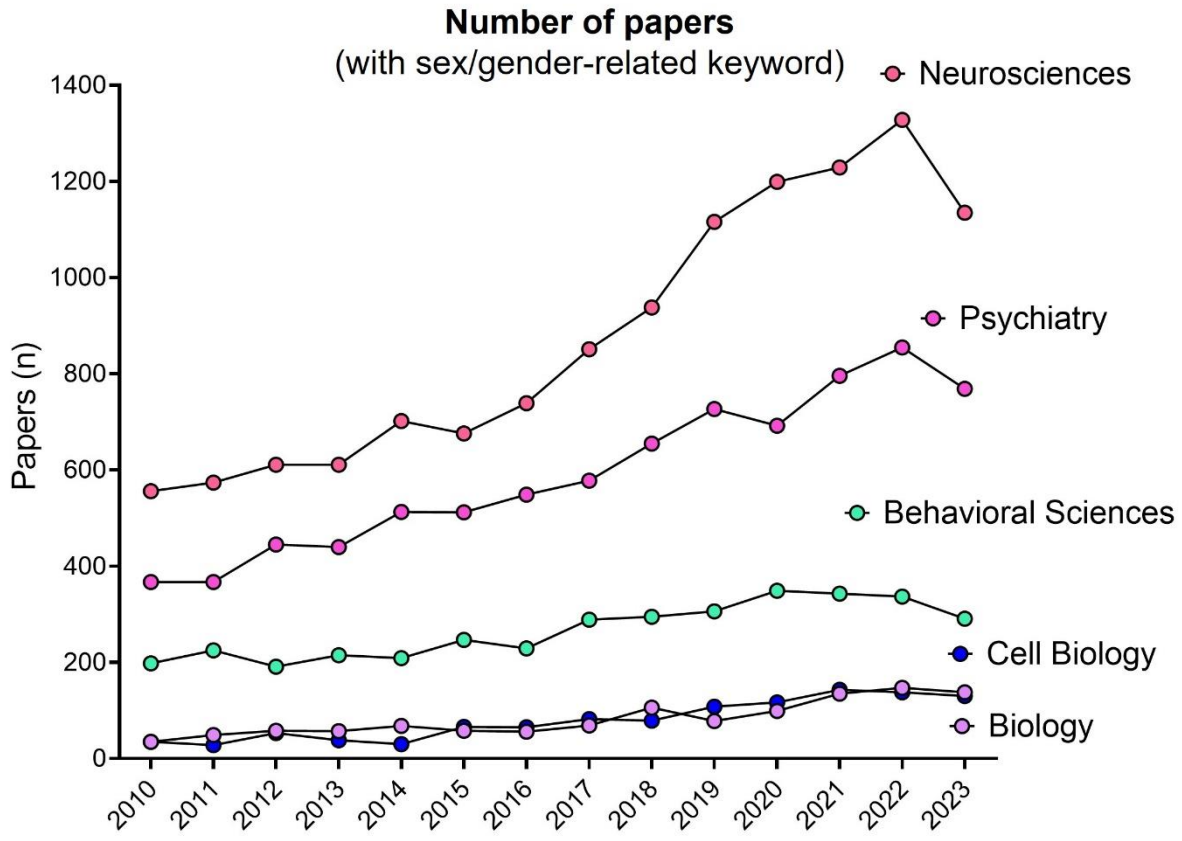

Fig. 3. Keyword co-occurrence networks in brain research. Note: The colors of circles are used to identify the clusters resulting from analyses of the relationships provided by the VOS Viewer software (red: disorders, blue: complex, green: method, purple: addiction, cluster size: frequency).