Review

Not peer-reviewed version

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Posted Date: 25 June 2024

doi: 10.20944/preprints202406.1772.v1

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Review

Sex Differences in Human Brain Networks from the Perspective of Small-World Properties

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Abstract: Based on non-invasive neuroimaging techniques and graph theory-based network analyses, many researchers have tried to use small-world network model to elucidate sex differences in the brain. This manuscript aims to compile the related research findings from the past few years and summarize the sex differences in human brain networks from the perspective of small-world properties. We reviewed published reports examining altered small-world properties in both the functional and structural brain networks between males and females. Based on four patterns of altered small-world properties proposed--randomization, regularization, stronger small-worldization and weaker small-worldization, we found that current results point to a significant trend toward more regularization in females and more randomization in males in the functional brain networks. As for particular topological properties, the most consistent findings include a significant shift toward higher global efficiency in males and higher local efficiency in females in the functional network studies. On the other hand, there seems to be no consensus to date on the sex differences in small-world properties of the structural brain networks. Nevertheless, we noticed that the sample sizes in many published studies are limited, and future studies with larger samples are warranted to obtain more reliable results. We anticipate that the conclusions in this manuscript will contribute to a deeper understanding of neurobiological mechanisms underlying the sex differences in the brain.

Keywords: neuroimaging; brain network; brain connectome; sex difference

1. Introduction

Previous studies have revealed that there are significant differences between the brains of males and females, which become evident in both structure and function [1–9]. For instance, Cosgrove et al. [5] indicated that brain volume was greater in men than women, while women had a higher percentage of gray matter and men a higher percentage of white matter when controlling for total volume. Moreover, global cerebral blood flow was higher in women than in men. Goldstein [6] observed that women had larger volumes relative to cerebrum size particularly in frontal and medial paralimbic cortices, and men had larger volumes relative to cerebrum size, in frontomedial cortex, the amygdala and hypothalamus. Sun et al. [9] found that males had higher overall white matter (WM) fiber numbers. Gong et al. [10] found that women showed higher cortical functional connectivity (FC) mostly in the left hemisphere, whereas men had higher connectivity in the right. Published studies had shown greater local clustering in cortical anatomical networks in females as compared with males [9,11–13]. Gur et al. [7] ,Tunç et al. [14] and Ingalhalikar et al. [2] reported that males had greater intrahemispheric connectivity (within both hemispheres), enhanced modularity and transitivity, whereas females had higher interhemispheric connectivity and cross-module participation. Wang et al. [15] observed that significantly higher nodal efficiencies of the males were found in several brain areas of limbic and paralimbic regions, including hippocampus,

 doi:10.20944/preprints202406.1772.v1

parahippocampal gyrus, amygdala, and cingulated gyrus. Apart from the neuroanatomical differences, it is well-established that sex differences in behaviors and cognitive performance have been fully demonstrated as well. A number of reported research results [1,7,8,16–30] ~~have~~ confirmed that females had advantages in language (such as reading achievement, writing abilities and verbal fluency), episodic memory and social cognition tasks, and males performed better on spatial processing, motor speed and mathematical abilities. For example, Asperholm et al. [20] suggested there was a female advantage for remembering faces, odors, tastes and colors, and a male advantage in more spatial tasks such as abstract images and routes. Furthermore, when using subnetworks that were defined over functional and behavioral domains, Tunç et al. [14] observed increased structural connectivity related to the motor, sensory and executive function subnetworks in males. And in females, subnetworks associated with social motivation, attention and memory tasks had higher connectivity. However, the neurobiological mechanisms of these sex-based differences in the brain remain incompletely understood, which deserve further exploration in future studies.

In recent years, non-invasive neuroimaging techniques and graph theory-based network analyses have been widely used and proposed to be powerful methods for characterizing individual differences in brain structures and functions [31–35]. In such a framework, the brain can be modelled as a complex network based on both structural and functional neuroimaging techniques. The widely used structural neuroimaging techniques include, for example, T1-weighted images (T1WI) [36] and diffusion-weighted imaging (DWI)/diffusion tensor imaging (DTI) [37]. The functional neuroimaging techniques include functional magnetic resonance imaging (fMRI) [38], electroencephalography (EEG) [39], and magnetoencephalography (MEG) [40]. Multiple topological properties of the constructed structural and functional brain networks can be then computed to reflect the changes in segregation and integration in brain systems, such as Cp (clustering coefficient), Lp (characteristic path length), γ (normalized clustering coefficient), λ (normalized characteristic path length), Eglob (global efficiency), and Eloc (local efficiency) (**Table 1**) [35,41]. Compared to traditional regions of interests (ROIs)- or voxel-based analysis, it was suggested that large-scale network analyses based on such a framework could better detected the connectivity in the brain, especially the interactions among different brain subsystems rather than a traditional regional or voxel-based analysis [42].

Specially, compared with random or regular networks, the structural/functional human brain networks are thought to show an optimal balance between the segregation and integration of information processing, which is known as "small-worldness" [43–47]. Generally, based on graph theory, it is known that regular networks contain many local links and are marked by a high Cp (accompanied by a higher γ and a higher Eloc) and a high Lp (accompanied by a higher γ and a lower Eglob); random networks contain many long-distance links and are marked by a low Cp and a low Lp; and small-world networks (e.g., typical brain networks) contain many local links and a few long-distance links (so-called shortcuts) and are marked by a high Cp and a low Lp. Based on the perspectives of segregation and integration, any deviation of the brain networks from the optimal small-world organizations were then thought to reflect disrupted brain structure or functioning, which can be classified into four distinct patterns: namely, randomization, regularization, stronger small-worldization and weaker small-worldization (**Table 2**) [42]. Randomization, which means turning from a small-world network to a relatively random network, is characterized by at least one altered measurement of the following conditions: decreased Cp, decreased γ, decreased Eloc, decreased Lp, decreased λ, or increased Eglob. Regularization, which means turning from a small-world network to a relatively regular network, is characterized by at least one altered measurement of the following conditions: increased Cp, increased γ, increased Eloc, increased Lp, increased λ, or decreased Eglob. Stronger small-worldization, which means turning from a small-world network to a relatively stronger small-world network, is characterized by not only at least one altered measurement of the following conditions (increased Cp, increased γ, or increased Eloc) but also at least one altered measurement of the following conditions (decreased Lp, decreased λ, or increased Eglob). Weaker small-worldization, which means turning from a small-world network to a relatively weaker small-world network, is characterized by not only at least one altered measurement of the

 doi:10.20944/preprints202406.1772.v1

following conditions (decreased Cp, decreased γ, or decreased Eloc) but also at least one altered measurement of the following conditions (increased Lp, increased λ, or decreased Eglob).

Table 1. Summary of common measures of small-world properties and their definitions.

	Measure	Full name	Definition
Measure of segregation	Cp	clustering coefficient	The probability that neighboring nodes that are also interconnected with other neighboring nodes.
	γ	normalized clustering coefficient	The normalized Cp, which is calculated for the average Cp of 100 matched random networks that preserve the same number of nodes and edges as the real network.
	Eloc	local efficiency	Eloc ensures functionally segregated processing, and measures how efficiently information is exchanged at the local level.
Measure of integration	Lp	characteristic path length	The average distance from one node to any other node in the network, expressed as the number of links that must be travelled.
	λ	normalized characteristic path length	The normalized Lp, which is calculated for the mean Lp of 100 matched random networks that preserve the same number of nodes and edges as the real network.
	Eglob	global efficiency	Eglob is a network statistic that is proportional to the average length of the shortest paths, characterizing long-range integration of the overall network.

Table 2. Four distinct alteration patterns from the perspective of small-world properties.

Pattern	Topological properties						
	Cp	γ	Eloc		Lp	λ	Eglob
Randomization	↓	↓	↓	And/or	↓	↓	↑
Regularization	↑	↑	↑	And/or	↑	↑	↓
Stronger small-worldization	↑	↑	↑	And	↓	↓	↑
Weaker small-worldization	↓	↓	↓	And	↑	↑	↓

Past clinical studies using various neuroimaging methods have documented that many common psychiatric disorders (e.g., schizophrenia) are associated with significant alterations in large-scale brain networks from the perspective of small-world properties. For example, Ma et al. [48] found that at rest, the patients with schizophrenia group retained the smaller Cp, γ, and shorter path length in functional brain networks than the healthy control group, which suggested that the functional connectome in schizophrenia group had a trend toward randomization. The majority of the other published researches have also consistently demonstrated that the patients with schizophrenia exhibit "more randomization" in functional brain networks [49–54]. On the other hand, most research results on the functional brain networks in patients with bipolar disorder (BP) have indicated more regularization. For instance, Spielberg et al. [55] observed a trend toward regularization characterized by greater Cp and worse Eglob for right amygdala across BP participants. Furthermore, many studies on the structural or functional brain networks in patients with major depressive disorder (MDD) have also suggested significant deviations from the optimal small-world topologies [56–58]. For instance, Chen et al. [59] found that structural brain networks in the MDD patients showed more regularization characterized by increased Cp, Eloc and Lp. Overall, these findings illustrate the disparities in the pathogenesis of various psychiatric disorders from the perspective of small-world brain topology, thereby enhancing our comprehension of these psychiatric disorders.

In the field of research on possible sex differences in human brains, many researchers have also tried to use the small-world network model to elucidate differences in small-world properties of brain networks between males and females. For example, based on the fact that the hemispheric morphological networks showed small-world properties and a high efficiency, the results of Choi et al. [60] indicated that brain network analysis using morphological features provided insights into the understanding of hemispheric asymmetry related to sex. Gong et al. [10] found females showed both higher overall Eglob and Eloc than males, which represented stronger cortical connectivity in females. It provided direct evidence for this hypothesis from the study of Gur et al. [61] that supposed women might make more efficient use of the available WM. Gong and his colleagues also reported that females showed greater efficiency in two well recognized language-related regions, which might contribute to explaining the previously observed female advantage in language. Furthermore, they found males had a rightward laterality of superior parietal gyrus, which might indicate men's advantage in visuospatial function. Additionally, Spalek et al. [62] observed that males showed higher values in brain connectivity that could point to an increased functional segregation in males, which proved females higher inter-wiring of brain regions or a more efficient way of communication. This conclusion might provide a neural correlate for sex-dependent memory performance differences that females performed better on the episodic memory recall because successful memory retrieval requires the conjunct activation of a network of brain regions (the less functional segregation, the higher interconnectedness) [63]. However, there are still shortcomings in current research. To be specific, in several published studies on functional network: Gong et al. [10] showed stronger small-worldization in females, Choi et al. [60] supported more regularization in male and more randomization in females, Yang et al. [1] and Yan et al. [11] observed more regularization in females, and so on. These results are not completely consistent and even conflict with each other. Therefore, it is necessary to review the previous studies to investigate whether there are consistent conclusions, while there have been no relevant reviews published in recent years to our knowledge.

To fill the gap mentioned above, this review is designed to narratively summarize the published studies on sex differences in human brain networks from the perspective of small-world properties. We aimed to compile the research findings from the past few years, focus on the investigation of sex differences in the small-world properties of both structural and functional brain networks, and discuss whether any widely accepted conclusions have been reached in this field. We incorporated all relevant structural and functional brain network studies conducted on healthy individuals into our analysis. We anticipate that the results will contribute to a deeper understanding of sex differences in the brain.

2. A Review of Published Studies

We summarized the relevant research progress in the following paragraphs based on search results from Web of Science (WoS). The searching strategy is as follows: "("gender difference*" OR "sex difference*" OR "gender effect*" OR "sex effect*" OR "gender related*" OR "sex related*" OR "gender dependent*" OR "sex dependent*") AND ("global efficiency" OR "local efficiency" OR "characteristic path length" OR "clustering coefficient")", and all of the reviewed articles are published before May 30th, 2024. We carefully checked the searched literature and excluded studies not conducted in healthy participants.

2.1. Studies on Functional Brain Networks

According to the search criteria, we found a total of seven studies on sex differences in functional brain networks, of which 3 used resting-state fMRI (rs-fMRI), 3 used EEG and 1 used rs-MEG (**Table 3**).

Based on the seven functional network studies, we found five data sets from seven studies were nearly consistent that reported a shift toward regularization in females compared with males [64–68]. Specifically, in 2013, Wu et al. [66] reported higher Lp, λ, Cp and Eloc in females but lower Eglob than males (more regularization in females). Afterward, in 2019, Dimech et al. [64] scanned 49 order adults, including 29 women and 20 men. They found increased Eloc and lower Eglob in females (more regularization in females than males). In addition, with EEG signals Jalili [67] supported female brains showed greater Eloc and lower Eglob in the right hemisphere than male brains (more regularization in females). Using a high-density resting state electroencephalography (rs-EEG), Kavčič et al. [65] in 2023 studied 10 males and 17 females (aged 5-18 years). They observed in the beta frequency band, females exhibited higher interhemispheric strength, Lp, and Cp than males (more regularization in females). Qian et al. [68] demonstrated that females showed higher Eloc in delta band when focusing on the search task in females than males by constructing multi-frequency EEG networks (more regularization in females). Moreover, Wu et al. [66] and Jalili [67] found similar results that males showed higher Eglob than females, which suggested a shift toward more randomization in males than females.

However, we noticed that the findings in several other published studies were not consistent with the above reports. Three data sets from 7 studies showed no significant difference [15,65,69]. In detail, by high-density EEG Kavčič et al. s65] observed that in the alpha frequency band between males and females there were no significant differences but seems more regularization in males (higher Lp, Cp, σ than females) because the data sets sample size of the test data set was very low. Besides, in the study by L. Wang and colleagues [15], they researched 20 healthy human volunteers (10 males and 10 females) and found though the females had slightly reduced global efficiencies, but slightly increased local efficiencies compared with the males, the group differences were not statistically significant. In addition, Shumbayawonda et al [69] investigated 220 healthy volunteers. They found that using transfer entropy (TE), both males and females have similar efficiencies.

More notably, we find that the findings in several other published studies are not consistent with the above reports. For example, using rs-fMRI, Cieri et al. [70] noticed females in normal controls showed significantly lower Eglob, Eloc, and Cp, as well as significantly higher Lp (weaker small-worldization in females).

In summary, the majority of the published studies mentioned above suggest that there is a prominent trend that is a more regularization in females and a more randomization in males in small world properties. However, no significant or even conflict results have been also reported in several studies. Results of these related studies were summarized in **Table 3**.

Table 3. Summary of related studies on functional brain networks.

Reference	Sample	Neuroimaging methods	Main findings on sex differences in brain networks
[15]	10 males and 10 females (aged 21-25 years)	rs-fMRI	No significant difference in Eglob and Eloc between males and females (greater Eglob in male and greater Eloc in female)
[64]	49 older adults (age mean= 67.25y ,29 women).	rs-fMRI	More regularization in females (Increased Eloc and lower Eglob in females; higher Eglob in males)
[65]	10 males and 17 females (aged 5-18years)	high-density rs-EEG	Alpha frequency band: no differences (low samples) but seems more regularization in males (higher Lp, Cp, σ); beta frequency band: more regularization in females (higher Cp, Lp, σ, Eglob)

[66]	24 boys and 36 girls (5.7–18.4 years)	rs-fMRI	More regularization in females (higher Lp, λ, Cp and Eloc but lower Eglob)
[67]	24 females (mean age 39) and 21 males (mean age 45)	EEG	More regularization in females' right-hemispheric (greater right-hemispheric Eloc and lower Eglob)
[69]	220 healthy volunteers (aged 7-84 years)	rs-MEG	Similar efficiencies between both males and females
[68]	35 females and 35 males (mean age± SD = 22.4 ± 2.3 years)	EEG	More regularization in females (higher Eloc in delta band when focusing on the search task)

2.2. Studies on Structural Brain Networks

According to the search conditions, we found a total of nine studies on sex differences in structural brain networks, of which 3 used T1WI and 6 used DWI/DTI (**Table 4**).

Based on the nine structural network studies, we found that results from 9 studies showed different conclusions in small world properties between males and females. These studies include 1 report of stronger small-worldization in females [10], 1 report of stronger small-worldization in males and weaker small-worldization in females [9], 1 report of more regularization in males and more randomization in females [60], 1 report of more regularization in males [62], 1 report of more randomization in females [8], 1 report of more randomization in males [1], 1 report of more regularization in females [11], and 2 report of no significant differences [71,72].

In 2009, Gong and colleagues recruited [10] 47males and 48 females and found that women showed greater overall cortical connectivity both locally and globally as well as lower integrated cost compared with men, which meant women had higher Eglob and lower Eloc (stronger small-worldization in females).

However, we noticed that there were some different findings as follows. For example, using DTI technique and graph theory methods, Sun et al. [9] in 2015 reported a more economical small-world architecture in females regardless of scan time point. To be specific, males showed greater Eglob, lower Lp and increased Cp (stronger small-worldization in males) as well as females showed higher Lp and decreased Cp (weaker small-worldization in females).

Afterward, in another study, using the T1-weighted magnetic resonance imaging scans of 150 females and 135 males, in 2020 Choi et al. [60] studied a cortical thickness-based brain structural covariance network named hemispheric morphological network and supported males showed greater Eloc and lower Eglob in the left hemispheric network(more regularization in males),while females showed greater Eglob and lower Eloc in the left hemispheric network (more randomization in females). Moreover, Spalek et al. [62] observed that males showed higher values in weighted transitivity on node-level (higher Cp) and increased segregation compared to females (more regularization in males). Additionally, using surface-based morphometry and structural covariance (SC) analysis, Shi et al. [8] constructed structural covariance networks (SCN) based on cortical volume. They found that females had higher number of SC connections which meant superior network integration, and high Eglob of SCN compared with males (more randomization in females).

There are other studies reported opposite conclusions as well. On the one hand, Yang et al. [1] suggested that males showed higher nodal strengths throughout the brain, greater global and local structural covariance as well as higher Eglob (more randomization in males). On the other hand, by constructing weighted cortical networks from 72 young healthy participants (including 38 females and 35 males), Yan et al. [11] found that females had greater Eloc than males (more regularization in females). They also found smaller brains showed higher Eloc in females but not in males.

Furthermore, Kim et al. [72] found that there were no significant differences in the structural connectivity and global network properties between boys and girls. Koenis et al. [71] reported that adolescents with higher intelligence had higher Eglob and Eloc but there were no significant differences between boys and girls at each time-point separately for FA-weighted global and local efficiency. They concluded the associations between global and local efficiency of the brain with intelligence revealed no evidence for quantitative or qualitative genetic sex differences.

In summary, we observed a number of different conclusions in the aforementioned studies of structural network. In conclusion, there seems to be no consensus to date on the sex differences in small-world properties of the structural brain networks. Results of these related studies were summarized in **Table 4**.

Table 4. Summary of related studies on structural brain networks.

Reference	Sample	Neuroimaging methods	Main findings on sex differences in brain networks
[10]	47 males and 48 females (aged 19–85 years)	DTI	Stronger small-worldization in females (higher Eglob and Eloc)
[1]	A healthy sample of 28,821 from UKBB (15,073 females,13,748 males)	(based on cortical thickness) T1WI	More randomization in males (higher Eglob)
[9]	Baseline:28 females (aged 18-25 years) and43 males (aged 22-53y) Longitudinal:15 females (aged 26-61 years) and 13 males (aged 29-53y)	DTI	Stronger small-worldization in males (greater Eglob, lower Lp and increased Cp); weaker small-worldization in females (higher Lp and decreased Cp)
[62]	264 males and 391 females (aged 18-35 years)	DWI	More regularization in males (higher Cp)
[60]	150 females and 135 males (aged 22-36 years)	(based on cortical thickness) T1WI	More regularization in males (greater Eloc and lower Eglob in the left hemispheric network); more randomized in females

			(greater Eglob and lower Eloc in the left hemispheric network)
[8]	111 females and 61 males (aged 20-65 years)	(based on cortical volume) T1WI	More randomization in females (higher Eglob of structural covariance networks)
[72]	99 children (54% boys, aged 6-11 years)	DTI	No significant differences in the structural connectivity and global network properties between male and female children
[11]	38 females (aged 18-24 years) and 35 males (aged 18-27y)	DTI	More regularization in females (greater Eloc)
[71]	310 twins and their older siblings (158 boys and 172 girls but 20 of them with poor quality DTI scan); mean ages: 10, 13, and 18 years	DTI	No significant sex differences

3. Discussion

The aim of this manuscript is to summarize published findings on the sex differences in structural and functional human brain networks from the perspective of small-world properties. Based on 4 patterns of altered small-world properties proposed by Suo et al. [42] --randomization, regularization, stronger small-worldization and weaker small-worldization, the most prominent trend in the functional network studies reviewed here is more regularization in females and more randomization in males. However, it seems that no consistent alterations were reported in structural brain networks.

3.1. Sex Differences in Functional Brain Network

Large proportions of the reported neuroimaging techniques were rs-fMRI and EEG. Of the 3 studies using rs-fMRI, 2 studies consistently reported more regularization in females [64,66], 1 study reported more randomized in males [66], and 1 study reported no significant difference [15] between mate and female while characterized by a litter greater Eglob in male and a little greater Eloc in female, which showed a trend toward a litter more regularization in females and more randomized in males. The conclusions of studies using rs-fMRI are almost not contradictory. Of the 3 studies using EEG, 3 studies consistently reported more regularization in females [65,67,68], 1 study reported more randomized in males [67], and 1 study reported no difference but seems a little more regularization in males [65].

The global efficiency of a network can be conceptualized as the efficiency of parallel information transfer in the network [73], which can be thought to be a more robust measure of integration. High global efficiency reflects effective interactions or rapid transfers of information between and across remote cortical regions that are believed to form the basis of cognitive processes. In the functional network studies, there are four studies that reported similar conclusions, which showed a shift toward higher Eglob in males [15,64,66,67,69]. Among these above, Wu et al. [66], Jalili [67] and L. Wang et al. [15] showed higher Eglob in males than females. Dimech et al [64] reported males had higher Eglob but they also found Eglob was negatively associated with cardiorespiratory fitness (CRF) in the default, frontoparietal control, and cingulo-opercular networks only in males. [69] [65] However, there are one study reported inconsistent conclusion that females' Eglob were higher than males. Specifically, Kavčič et al. [65] found females showed higher Eglob compared to males in the beta frequency band. [74]

The local efficiency is a measure of communication between nodes [74], which can be thought to be a more robust measure of segregation. High local efficiency implies the modularized information processing among nearby regions. Five studies also showed similar results: both observed females showed higher Eloc than males [15,64,66–68]. For instance, Wu et al. [66] and L. Wang et al. [15] showed higher Eloc in females than males. Dimech et al [64] found Eloc was positively associated with CRF in the default, frontoparietal control, and cingulo-opercular networks, which was more robust in male versus female older adults. Jalili [67] found female showed significantly greater right-hemispheric local connectivity (Eloc) than males. Qian et al. [68] also noticed that females showed higher Eloc in delta band when focusing on the search task in females compared to males.

Overall, the most prominent trend in the functional network studies about topological properties is a shift toward more randomization in males, and a shift toward more regularization in females.

3.2. Sex Differences in Structural Brain Network

In the structural network studies, large proportions of the reported structural neuroimaging techniques were DTI/DWI and T1WI. Of the 6 studies using DTI/DWI, 2 studies consistently reported no significant differences between different genders [71,72], 1 report of more regularization in males [62], 1 study reported stronger small-worldization in males and weaker small-worldization in females [9], 1 report of stronger small-worldization in females [10], and 1 study reported more regularization in females [11]. We observe the inconsistencies in above studies using DTI/DWI. Spalek et al. [62] observed that males showed higher Cp (increased segregation) and females showed higher interconnectedness. Sun et al. [9] suggested a predilection for global information integration (higher Eglob) in males and that Eloc failed to pass the significance level, which might be attributed to the strengthened bilateral intra-hemispheric connections. Gong et al. [10] found women showed a higher overall cortical connectivity. Yan et al. [11] found that females had greater local efficiencies than males in their cortical anatomical networks. The possible explanations might~~may~~ be that the brain size effect on local efficiency was~~is~~ significant in females but not in males [11], and that brain size had different effects on the morphologies of anatomical structures between males and females [61,75,76]. For example, women had a larger corpus callosum [75], which suggested greater interhemispheric connectivity [10]. We also infer that the reasons for different findings may be a consequence of different image acquisition methods, sample size, and different age distribution. The weighted transitivity (Cp) was negatively correlated with age in cohort of healthy young adults [62]. There were also changes in the underlying network organization that resulted in decreased local efficiency with age [10]. The different results might have something to do with designs of studies as well. Sun et al. [9] designed not only baseline study but also longitudinal follow-ups. Gong et al. [10] only used cross-sectional data therefore could be influenced by potential cohort effects.

Of the 3 studies using T1WI, 2 studies consistently reported more randomized in females [8,60], 1 study reported more randomized in males [1], and 1 study reported more regularization in males [60]. In detail, Yang et al. [1] reported that males had higher global efficiency than females, whereas Choi et al. [60] found females were more globally efficient in the left hemispheric network. Above two studies used the same methodology. We speculate that the reasons for different findings may be a consequence of sample size, different age groups, and the selection of the brain atlas.

In summary, in the structural network studies, there are three studies that reported similar conclusions, which showed a shift toward higher Eglob in females relative to males [8,10,60]. Among these above, Gong et al. [10], Choi et al. [60], and Shi et al. [8] showed higher Eglob in females than males.

These results are not consistent and even conflict with those studies mentioned in the last paragraph. Two studies reported similar conclusions. Sun et al. [9] showed males exhibited higher

 doi:10.20944/preprints202406.1772.v1

Eglob suggesting a predilection for global information integration which might be attributed to the strengthened bilateral intra-hemispheric connections. Yang et al. [1] found that males showed higher Eglob, as well as higher regional covariance (nodal strengths) in both hemispheres compared with females.

Two studies found that females showed higher Eloc than males [10,11]. In detail, Yan et al. [11] found that females had greater Eloc than males and smaller brains showed higher Eloc in females but not in males. There was also another published finding that supported similar conclusion. Lou et al. [77] found that phonemic decoding was also positively correlated with the Eloc of the reading network that was significantly relevant in girls, but no significant correlations were found in the boys group. And the phonemic decoding subtest is related to word reading efficiency. Another studies from Choi et al. [60] noticed that males showed higher Eloc than females.

Overall, there seems to be no consensus to date on the sex differences in small-world properties of the structural brain networks.

3.3. Possible Reasons for Inconsistent Findings

Here, we propose that the inconsistencies in previous studies (especially on structural networks) may be partly due to several reasons: sample size, different age groups, methodology alterations and so on.

First, we noticed that the sample sizes in some studies are relatively small, which might lead to less reliable results [15,65]. Test data set sample size was much smaller, therefore higher probabilities were less likely to be observed. Kavčič et al. [65] supported that they couldn't claim that any significant differences in graph metrics existed between sexes in the alpha frequency band in either of the data sets sample size of the test data set was very low (subgroup of only 10 males), therefore these results should be interpreted with caution. As a result of small sample size, we probably could not detect sex differences, which were observed in a larger validation data set.

Second, the sex differences in human brain networks of small-world properties may be associated with age. In the systematic review of Richmond et al. [78], they summarized that for SC, diffusion MRI findings indicated decreased clustering, increased Eglob and Eloc with age from the prenatal to late adolescent period (stronger small-worldization with age). The clustering coefficient, which is related to weighted transitivity [79] showed a decrease in younger age groups but an increase in older ages [80]. There was also some indication pointing to the development tendency toward a less economical topology with aging and there was a significant gender-time interaction on Cp. Specifically, males showed an insignificant increase of Cp whereas females exhibited a significant decrease [9]. However, Gong et al. [10] found that the aging network became less connected (cost more), an overall cortical connectivity became reduced, and the disruption of anatomical connectivity in aging might impair the functional integration between areas, which resulted in a decreased overall Eloc but a preserved overall Eglob in older people. Another study reported consistent result that network efficiency of functional networks reduced in normal aging using rs-fMRI techniques [81]. There is another study reported diverse conclusion. Henry et al. [82] found that Eglob had an opposite relationship with age by first decreasing and then increasing in the autism spectrum disorder (ASD) group. So, diseases could affect brain network topological properties.

Third, different methodology alterations may lead to different results. Inherent EEG limitations for studying functional connectivity should also be considered [65]. Using DTI, Ingalhalikar et al. demonstrated a male preponderance of intra-hemispheric connections bilaterally, whereas females only exhibited greater left-to-right frontal lobe connection [2]. Sun et al. [9] found that males showed higher Eglob. Their observation of more efficient global information transfer in males might be attributed to the strengthened bilateral intra-hemispheric connections. Based on DWI tractography [62], a one-to-one relationship between a given diffusion parameter and the underlying tissue structure was not possible [83,84].

Another limitation in the study of Shumbayawonda et al. [69] is the use of unbalanced numbers of subjects in groups. We also speculate that the apparent inconsistencies might be due to the different designs of studies. In addition, the sex differences in human brain networks of small-world properties may be associated with individual differences or psychological quality. From graph-based metrics, Wang et al. [85] detected significantly greater Eglob and Eloc but shorter Lp in the anatomical networks of the world class gymnasts as compared to healthy age and gender matched students, which showed champions had stronger small-worldization. Furthermore, most of the current studies mentioned were cross-sectional designs, which may result in some differences in diagnosis. Future studies can also benefit from longitudinal follow-ups. Further studies are needed to reconcile the apparent inconsistencies and confirm our findings.

3.4. Future Perspectives

As discussed above, future studies can be performed to obtain more reliable results on sex differences in human brain networks from the perspective of small-world properties, by enlarging the sample size, using more suitable methodology, and so on. This is especially necessary for structural brain networks as there seems to be no consensus conclusions in published studies to date.

Another valuable future direction may be to investigate the possible sex differences in the dynamic functional brain networks. In recent years, research on dynamic fluctuations of the functional brain network organizations so-called "dynamic functional brain network" has emerged [86–88]. Specially, some prior studies have promoted the "temporal small-world/dynamic small-world" model under such a framework, which could capture important information ignored by traditional "static" brain network model [89–91]. However, little is known about the possible sex differences in brain networks from the perspective of "dynamic" small-world properties, which deserves further investigations.

3.5. Limitations

This study has several limitations. First, the differences in preprocessing steps and analytical methods can produce inconsistent results, and thus the accurate integration of results across different studies is difficult. Second, some published studies might have been missed during the literature search because of the chosen keywords. Finally, the current knowledge is much limited on possible relationships between the sex differences in human brain networks from the perspectives of four patterns of altered small-world properties and several disorders. The number of studies is still limited to our knowledge, and more studies may be needed in the future to investigate the sex differences in human brain networks from the perspective of small-world properties.

4. Conclusions

In summary, this manuscript reviewed the published studies regarding the possible sex differences in human brain networks from the perspective of small-world properties. We found that most of the current results point to a significant trend toward more regularization in females and more randomization in males in the functional brain networks. On the other hand, there seems to be no consensus to date on the sex differences in small-world properties of the structural brain networks. We anticipate that the conclusions in this manuscript will contribute to a deeper understanding of neurobiological mechanisms underlying the sex differences in the brain. Nevertheless, we noticed that the sample sizes in many published studies are limited, and future studies with larger samples are warranted to obtain more reliable results.

Author Contributions: YZ and YL conceived the idea and structured the manuscript. YZ and YL drafted the manuscript. YZ and YL designed the figures and tables. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Scientific Research Launch Project for new employees of the Second Xiangya Hospital of Central South University (to YL), the Health Research Project of Hunan Provincial Health Commission (W20243225 to YL), and the National Natural Science Foundation of China (82201692 to YL).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: None.

Conflicts of Interest: The authors declare no conflict of interest.

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