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Research Article

Analysis of Gender Differences with Functional Connectivity and Default Mode Network and Fronto-parietal Network*

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Abstract

Gender is known to play a critical role in the brain's anatomy, function, and also in human behavior. Identifying differences in functional connectivity between male and female brains will help explain the prevalence and symptomatology of many neurological and psychiatric conditions. Imaging of the brain during rest reveals spontaneous low-frequency fluctuations (<0.1 Hz) that have a temporal correlation between functionally related areas in the fMRI signal. These correlations, called functional connectivity (FC), were obtained using seed to voxel analysis. FC analyzes were compared between male and female brains, including 50 healthy individuals (25 females, 25 males) using the right hand between aged 19 to 41 years old, using resting state functional magnetic resonance imaging (rs-fMRI). Data in this study was obtained from the Newyork_a data set under the 1000 Functional Connectomes Project shared publicly. In our study, gender differences in the default mode network, which is shown as having a central role among the rest state networks, and in the fronto parietal network that best reflects the cognitive network, were examined. In some seed regions of our study, regions showing higher FC were found in both female and male. While the seed regions showing positive correlation in DMN are MPFC and LP (L), the seed region showing negative correlation is LP (L). The seed regions that show positive correlation in FPN are LPFC (L), LPFC (R) and PPC (L), while the seed regions that show negative correlation are LPFC (R), PPC (L) and PPC (R). As the result of our study, the most important finding is that all of our regions with positive correlation were associated with the cerebellum. Our regions associated with regions that show negative correlation showed scattered settlement in the brain. Our study revealed that gender differences in brain networks should be considered when examining neurological and neuropsychiatric disorders. In addition, our results have shown that gender differences in brain networks require more research.

Keywords: fMRI, resting state, gender differences, functional connectivity.

Varsayılan Mod ve Fronto Parietal Ağlarında Fonksiyonel Bağlanabilirlik ile Cinsiyet Farklılıklarının İncelenmesi

Öz

Cinsiyetin beynin anatomisinde, işlevinde ve aynı zamanda insan davranışlarında kritik bir rol oynadığı bilinmektedir. Erkek ve kadın beyinleri arasındaki fonksiyonel bağlantıdaki farklılıkları belirlemek, birçok nörolojik ve psikiyatrik durumun prevelansını ve semptomolojisini açıklamaya yardımcı olacaktır. Dinlenme sırasında beynin görüntülenmesi, fMRG sinyalinde fonksiyonel olarak ilişkili alanlar arasında geçici olarak korelasyona sahip olan spontan düşük frekanslı dalgalanmalar (<0.1 Hz) ortaya çıkarır. Fonksiyonel bağlanabilirlik (FC) olarak adlandırılan bu korelasyonlar, tohum voksel analizi kullanılarak elde edilmiştir. FC analizleri, dinlenme durumu fonksiyonel manyetik rezonans görüntüleme (dd-fMRG) kullanılarak 19 ila 41 yaş arasındaki sağ elini

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kullanan 50 sağlıklı birey (25 kadın, 25 erkek) dahil edilerek kadın ve erkek beyinleri arasında karşılaştırılmıştır. Bu çalışmadaki veriler, herkese açık olarak paylaşılan 1000 Functional Connectomes Project kapsamındaki Newyork_a veri setinden sağlanmıştır. Çalışmamızda dinlenim durumu ağları arasından merkezi bir rolü olduğu gösterilen ve en çok çalışılan ağ olan varsayılan mod ağında ve bilişsel ağı en iyi yansıtan fronto parietal ağında cinsiyet farklılıkları incelenmiştir. Çalışmamızın bazı tohum bölgelerinde hem kadınlarda hem erkeklerde daha yüksek FC gösteren bölgeler bulunmuştur. DMN'de pozitif korelasyon gösteren tohum bölgeleri MPFC ve LP (L) iken, negatif korelasyon gösteren tohum bölgesi LP (L)'dir. FPN'de pozitif korelasyon gösteren tohum bölgeleri ise LPFC (L), LPFC(R) ve PPC (L) iken, negatif korelasyon gösteren tohum bölgeleri ise LPFC (R), PPC (L) ve PPC (R)'dır. Çalışmamızın sonucunda en dikkat çekiçi olan bulgu pozitif korelasyon gözlemlenen tüm bölgelerimizin beyincik ile ilişkili olmasıdır. Negatif korelasyon gösteren bölgeler ile ilişkili bölgelerimiz beyinde dağınık yerleşim göstermiştir. Çalışmamız nörolojik ve nöropsikiyatrik bozukluklar incelenirken beyin ağlarındaki cinsiyet farklılıkları göz önünde bulundurulması gerektiğini ortaya koymuştur. Ek olarak, sonuçlarımız beyin ağlarındaki cinsiyet farklılıklarının daha fazla araştırma yapılması gerektiğini göstermiştir.

Anahtar Kelimeler: fMRG, dinlenim durumu, cinsiyet farklılığı, fonksiyonel bağlanabilirlik.

1. Introduction

Gender differences have become a topic of interest in many areas of neuroscience due to differences in the behavior of humans and non-human species [1]. Although there are many similarities in male and female brains, it is known that gender plays a critical role in the anatomy, function, and also of human behavior in the human brain [2]. Differences in the anatomical structure of the brain have been documented in numerous studies [3]. However, there are different results among the studies on functional connection differences [4,5]. Identifying differences in functional connectivity between male and female brains will help explain the prevalence and symptomatology of many neurological and psychiatric conditions.

Development in neuroimaging provided the opportunity to evaluate the differences between brain structure, function and chemistry in males and females. Resting state functional magnetic resonance imaging(rs-fMRI) is a non-invasive neuroimaging method that emerges as a powerful tool for evaluating the functional connectivity patterns of the human brain and reveals large amplitude spontaneous low frequency (<0.1 Hz) fluctuations that temporarily correlate between functionally related areas [6].

Evaluation of resting state networks allows to study the internal functional architecture of the human brain, also called functional connection [4]. Functional connecting is defined as a temporal correlation in BOLD signal fluctuations between two or more anatomically different regions [7]. Functional connectivity is interpreted as an indirect measure of neuronal activity.

The first focus of studies evaluating gender differences is to evaluate the structural differences in the brain. Once structural differences are identified, key factors such as gender are expected to have an impact on functional connectivity based on their strong relationship with the underlying anatomy [8]. Important evidence supporting the idea that gender makes a difference in brain connectivity has been reported in recent neuroimaging studies. In addition, Weissman-Fogel and colleagues were unable to observe gender differences in RSNs [5]. When we evaluate the studies, it is draw the attention that the gender differences in the adult brain should be investigated further.

In our study, gender differences in DMN and FPN, which was shown to have a central role among the rest state networks, were examined. DMN is a brain region containing precuneus / posterior cingulate cortex (PCC), medial prefrontal cortex(mPFC), and medial, lateral, and inferior parietal cortex. Although studies have shown that the activity of this network varies in depression, schizophrenia[10], autism[11], epilepsy[12], and alzheimer's disease[13], few studies have examined factors affecting the link of DMN activity in a healthy population. It is reported that women show more connections in gender differences in DMN, but the peripheral nodes of DMN have been reported to provide more connections in male than in female [14].

The fronto-parietal network (FPN) includes sections of the lateral prefrontal cortex and posterior parietal cortex. It is known to take part in a wide variety of tasks by initiating and modulating cognitive control abilities [15]. In addition, FPN is thought to contribute to directed attention and working memory [16]. The frontoparietal network is critical to our ability to coordinate behavior quickly, accurately and flexibly based on goals [17]. Many psychopathological conditions such as schizophrenia and attention deficit / hyperactivity disorder have been reported to affect the frontoparietal network [17]. There is a significant positive correlation between the functional integration of the frontoparietal network and the overall cognitive ability, which indicates that the power of the functional integration of the frontoparietal network and the rest of the brain is crucial to support cognitive functionality [18]. Cservenka et al. In their study using task-based fMRI, they stated that male showed stronger activation in FPN in adolescents and adults than female [19]. However, Filippi et al. argues that gender differences are more pronounced in the cognitive domain than in sensory networks [20]. Therefore, in our study, DMN which reflects the rest state networks the most, and FPN which best reflects the cognitive network best, were investigated.

Given the significant gender-specific differences in the prevalence of most neuropsychiatric disorders, and the different findings between studies with healthy participants suggest that more research needs to be made to better understand the effect of gender on brain structure and function. The strength and diversity of gender-related effects on brain function and the fact that there are different findings between studies on this subject have been the motivation of this study. With this study, gender differences in brain connectivity in DMN and FPN in healthy adults aged 19-41 years were investigated.

2. Material and Method

2.1. Participant

The rs-fMRI data in this study was obtained from the Newyork_a data set under the 1000 Functional Connectomes Project shared publicly (http://fcon_1000.projects.nitrc.org/fcpClassic/FcpTable.html) [4].

In our study, only Newyork_a dataset was used to minimize variability between institutions, such as shooting conditions and scanning procedures.

This study included 50 healthy individuals aged 19-41. This age range is divided into two groups, male and female, each consisting of 25 healthy people. Average age and average movement information are given in Table 1. All the participants selected consist of right-handed people. The data have small head movements, functional images of each participant consist of 197 volumes and each volume consists of 39 slices. In the rs-fMRI shootings, the participants were told to remain in a state of rest with their eyes open.

Table 1. Average age and average movement information of the participants

Group	Age (Standard deviation)	Ortalama Hareket (Standard deviation)
Female	26,692(±4,5992)	0,1191(±0,0468)
Male	27,275(±5,6864)	0,1178(±0,03733)

2.2. Pre-processing

The pre-processing steps were made with MATLAB based Statistical Mapping software through the CONN program (SPM8; www.fil.ion.ucl.ac.uk/spm/software/spm8/) and include the following steps.

(1) Initially, considering the factors that show the balance of the MR signals and the adaptation of the subjects to the conditions, the first 5 volumes were ejected.
(2) Slice timing correction was made to eliminate the time difference between the slices.
(3) Realignment was performed to correct motion-induced artifacts in functional data and to minimize possible movements during recording.
(4) In order to associate the participant's anatomical images and functional images, functional-structural coregistration was performed.
(5) Spatial normalization was performed to compare the spatial positions of functional activation among subjects.
(6) Spatial smoothing was performed with a 6 mm full width at half maximum (FWHM) Gaussian core to reduce noise and increase the signal to noise ratio.

After the pre-processing, 0.01-0.1Hz band pass filter was applied in the balancing step to evaluate the marks in the range of 0.01-0.1Hz, which is the spontaneous oscillating resting frequency.

2.3. Seed to Voxel Analysis

The seed-based analysis is the first method adopted by Biswal to identify resting state networks [21]. Seed-based analysis is a model-based method that calculates the linear correlation of a seed region with voxels in the entire brain, thus providing a seed-based FC map [22]. The simplicity, interpretability, and intelligibility of this technique have made it a useful approach to rs-fMRI analysis.

Individual seed-voxel connectivity maps were created using the MATLAB based CONN fMRI Functional Connectivity Toolbox v18a (http://www.nitrc.org/projects/conn) [23].

2.4. Statistical analysis

All statistical analyzes were made with the T statistic and the F statistic using the CONN toolbox. A sample t-test for intra-group comparisons was used in both female and male groups with FDR-corrected ($p < 0.05$) significance thresholds. Two sample t-tests were used to compare the groups of female and male with the significance thresholds set at $P < 0.05$ with FDR correction.

3. Conclusions and Recommendations

In our study, gender differences were evaluated in 25 male and 25 female participants in DMN and FPN. Table 2 shows the positive and negative correlation results of two sample t-tests performed in the case of female>male for the significant regions in the resting state networks examined in the results of the functional connection analysis of the male and female groups. Positive and negative correlations were observed in both networks investigated. The region that shows the most difference in our study is LPFC (R) in FPN.

Table 2. Functional connectivity results, female> male: red filling, male>female: blue filling

Network	Seed region	Clusters (x,y,z)	Size	p-FWE	p-FDR	Associated regions (voxels)
DMN	MPFC	+04 -58 -52	138	0.009521	0.008642	Cerebelum 9 Right (60) Cerebelum 9 Left (37)
	LP (L)	-38 -72 -50	116	0.023136	0.026101	Cerebelum Crus2 Left (68) Cerebelum 7b Left (17)
	LP (L)	+50 -06 +04 -48 -06 +02 +46 +12 -18 +42 -26 +12	137 124 120 85	0.009942 0.016689 0.019634 0.087047	0.012152 0.012152 0.012152 0.041856	Temporal Pole Right (96) Central Opercular Cortex Right (84) Planum Polare Left (63) Heschl's Gyrus Right (58) Central Opercular Cortex Left (41) Parietal Operculum Cortex Right (32)
FPN	LPFC (L)	-30 -76 -50	170	0.002382	0.002507	Cerebelum Crus2 Left (67) Cerebelum 7b Left (36)
	LPFC(R)	-32 -78 -46 +46 -70 -48 -10 -88 -44	387 120 110	0.000002 0.017321 0.026428	0.000002 0.007922 0.008096	Cerebelum Crus2 Left (243) Cerebelum Crus2 Right (67) Cerebelum 7b Right (39) Cerebelum 8 Right (12)
	LPFC(R)	+50 +30 -12 -58 -46 +20	122 100	0.015937 0.40746	0.018798 0.024337	Supramarginal Gyrus, posterior division Left (75) Frontal Orbital Cortex Right (58) Frontal Pole Right (44) Parietal Operculum Cortex Left (19)
	PPC (L)	-36 -76 -52	269	0.000102	0.000130	Cerebelum Crus2 Left (192) Cerebelum 7b Left (18)
	PPC(L)	+40 +10 -10	490	0.0000	0.0000	Temporal Pole Right (174) Insular Cortex Right (135) Planum Polare Right (23)
	PPC(R)	+50 -42 +30	121	0.009441	0.014934	Supramarginal Gyrus, posterior division Right (134) Temporal Pole Right (63) Insular Cortex Right (38) Frontal Orbital Cortex Right (36) Angular Gyrus Right (13)

Seed regions showing positive correlation in DMN are MPFC and LP (L). A positive correlation with Cerebellum was observed in both seed regions. The region showing negative correlation in DMN is LP (L). Regions where negative correlation is most associated are TP r (Temporal Pole Right) and CO r (Central Opercular Cortex Right). In our study, both negative and positive correlations were observed in the LP (L) seed region. DMN region results are shown in Figure 1. Figure 1 shows the regions associated with MPFC and LP (L) seed regions, which show a positive correlation in the comparison of the female>male seen above. Figure 1 shows the regions associated with the LP (L) seed region, which shows negative correlation in the comparison of the female> male appearing below.

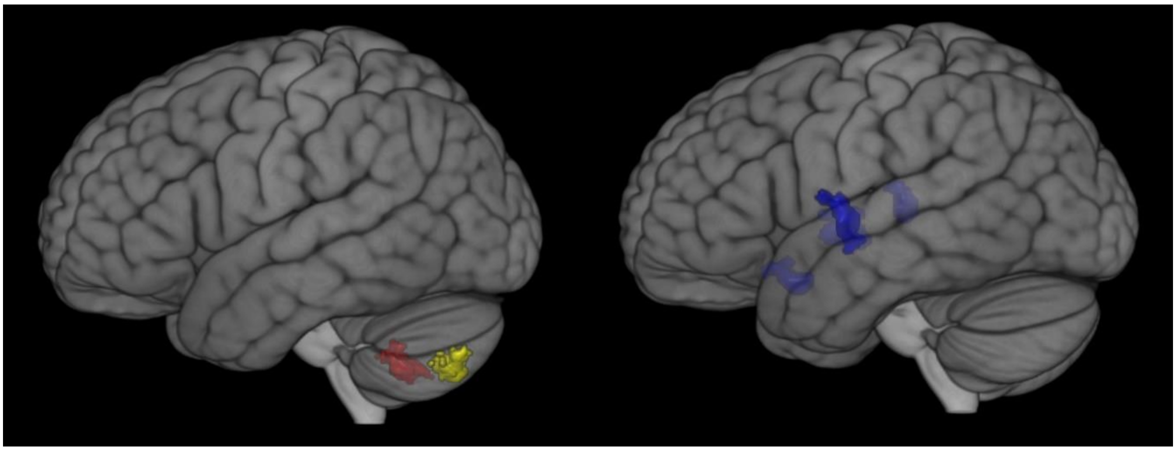

Figure 1. DMN region showing positive and negative correlations

Seed regions showing positive correlation in FPN are LPFC (L), LPFC (R) and PPC (L). Again, positive correlation with Cerebellum was observed in both seed regions. Seed regions showing negative correlation in FPN are LPFC (R), PPC (L) and PPC (R). Regions where negative correlation is most associated are pSMG l (Supramarginal Gyrus, posterior division Left) and FOrb r (Frontal Orbital Cortex Right). Figure 2 shows the regions related to LPFC (L), LPFC (R) and PPC (L) seed regions, which show a positive correlation in the comparison of female>male. Figure 3 shows the regions related to LPFC (R), PPC (R) and PPC (L) seed regions that show negative correlation in the comparison of female>male.

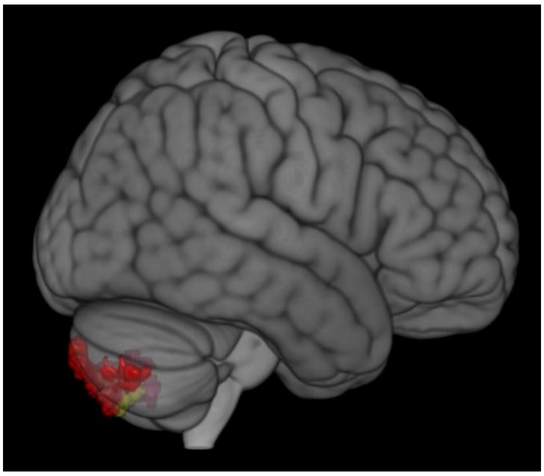

Figure 2. FPN Region positive correlation regions

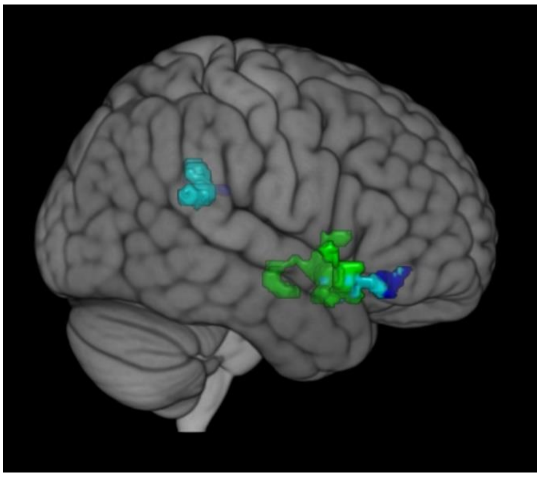

Figure 3. FPN Region negative correlation regions

In our study, we investigated the effect of gender differences on FC in healthy individuals aged 19-41. In previous studies, it has been stated that gender differences have an important effect in many areas such as emotion, memory, perception, and other cognitive domains [24]. However, variant results between studies have made it necessary to further examine functional gender differences in the brain. In our study, we used a limited age range to minimize the effects of age [20].

Studies have investigated the effect of gender differences in DMN, but different results have been found. Weissman-Fogel et al. stated that there was no gender difference [5]. Bluhm et al. investigated gender differences in DMN and stated that female had stronger FC in the medial prefrontal cortex in the posterior cingulate and pruneus regions, and that there was no high FC in male [25]. Biswal et al. studies, it was reported that there were significantly more connections in the medial prefrontal cortex and inferior parietal lobe in female in DMN [4]. These studies have demonstrated the importance of gender differences in brain functional connectivity and have revealed that more research is needed. In our study, positive correlation with MPFC and LP (L) was similar to literature. Gabriela Alarcón et al. reported that in their study with task-based fMRI, females showed a stronger functional link between the left mPFC and the right posterior cerebellum compared to males [26]. In our study, MPFC regions of women showed positive correlation with cerebellum.

In their study using Cservenka et al. task-based fMRI, they stated that males and adults exhibited stronger activation in FPN than females [19]. In their study with the task-based fMRI, Gabriela Alarcón et al. stated that females exhibit stronger functional connectivity in FPN and DMN than males [26]. In our study, positive correlation was observed in LPFC (L), LPFC (R) and PPC (L), and negative correlation in LPFC (R), PPC (L) and PPC (R) showed that more research should be done on this subject.

4. Conclusion

In our study, gender differences were examined in DMN, which is the most studied network and has the central role among rest networks, and FPN, which best reflects the cognitive network. While the seed regions showing positive correlation (female>male) in DMN are MPFC and LP (L), the seed region showing negative correlation (male>female) is LP (L). While the seed regions showing positive correlation in FPN are LPFC (L), LPFC (R) and PPC (L), the regions that show negative correlation are LPFC (R), PPC (L) and PPC (R). Regions associated with seed regions showing positive correlation in DMN and FPN are located in cerebellum, while regions showing negative correlation show scattered locations in different parts of the brain. These differences we obtained between the functionality of the male and female brains belonging to the young adult and middle-aged group may contain very important information and revealed the need for further research on this subject.

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