ALTERATIONS IN FUNCTIONAL CONNECTIVITY AND INTERACTIONS IN RESTING-STATE NETWORKS IN FEMALE PATIENTS WITH FUNCTIONAL CONSTIPATION

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Received: 12 May 2022 / Accepted: 9 July 2022 / Published online: 15 July 2022
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Abstract

Background Patients with functional constipation (FCon) have been reported with brain functional and structural abnormalities. However, no studies have been performed to investigate the differences in resting-state networks (RSNs) and changes in functional connectivity (FC) between RSNs in patients with FCon. Thus, the current study aimed to identify abnormal FC within and interaction between RSNs in patients with FCon to reveal the underlying neural mechanism.

Methods Functional MRI with independent component analysis was applied to investigate alterations in FC within and functional network connectivity (FNC) between RSNs including default mode- (DMN), basal ganglia- (BGN), salience- (SN), and left and right control executive-networks (LCEN/RCEN) in 39 female patients with FCon and 36 female healthy controls (HC). Patient Assessment of Constipation Quality of Life Scale (PAC-QOL) and Patient Assessment of Constipation Symptom Scale (PAC-SYM) were used to assess the constipation symptoms.

Results FCon patients had changed regional FC between different networks contributing to the abnormal FNC among RSNs compared with HC. Patients with greater stool syndromes had increased FNC of BGN-SN and DMN-LCEN, and patients with greater worries/concerns and PAC-QOL total score had reduced FNC of SN-RCEN. The greater strength changes in FC in prefrontal and parietal cortices were associated with higher negative emotion scores and greater rectal symptoms, respectively.

Conclusion The findings suggested that FCon patients had altered FC within and interactions between RSNs and the brain FC changes were associated with constipation symptoms and altered emotions.

Keywords Resting-state fMRI · Resting-state network · Functional connectivity · Independent component analysis · Functional constipation

Introduction

Functional constipation (FCon) is a type of functional gastrointestinal disorder (FGID) with a prevalence of 9.5% [1] and occurs with a higher incidence rate in female patients than in males (2.1:1). The incidence rate of constipation predominantly occurs in middle-aged individuals (> 30 years old), and there are occurrences of the disease in children and elderly subjects [2, 3]. FCon is characterized by infrequent bowel movements, difficulty in defecation, sensation of incomplete evacuation, and abdominal pain.
distension/pain [4], and it has a great impact on their physical and mental health.

FCon has been reported to be associated with brain functional and structural alterations in brain regions involved with emotional modulation (amygdala, insula-INS, orbitofrontal cortex-OF, hippocampus, anterior cingulate cortex), somatic and sensory processing (precentral gyrus, supplementary motor area), and self-referential processing [5–8]. A recent publication revealed sex-related differences in resting-state brain activity, and subsequent seed correlation analysis showed that female FCon had weaker functional connectivity (FC) of INS-OF, than males, which was negatively correlated with the anxiety in female FCon and with abdominal distension in male FCon [9]. Ma et al. reported abnormal visceral sensation processing in the central nervous system from the perspective of a large-scale brain white matter network [10]. However, few studies have been conducted to examine the association between FCon and resting-state networks (RSNs).

The measures of FC within and interactions between RSNs have been shown to be a better technique to represent intrinsic functional organization of the brain [11, 12], which has been applied in patients with FGID [13–16] and obesity [17] reporting abnormal interactions among RSNs. Irritable bowel syndrome (IBS), one of the subtypes of FGID, has been extensively studied. Patients with IBS showed greater activations in regions implicated in affective and attentional regulation, visceral/sensory processing, and alterations in FC within the default mode network (DMN), salience network (SN), control executive network (CEN), and basal ganglia network (BGN) [13, 15, 16, 18]. These studies revealed alterations in FC strength within RSNs and their association with symptoms in patients with IBS, and shed light on the possibility to examine abnormal FC within and interaction between RSNs in patients with FCon. One newly published paper investigated changes in brain dynamic FC and network topological organization in patients with FCon, and results showed that FCon patients manifested a lower occurrence rate and mean dwell time between DMN and CEN [19]. The correlations between RSNs are considered to be more vital than the activity of the RSNs themselves and to play a critical role in efficient, dynamic communication in the brain [11]. The altered interactions between RSNs, which might help in diagnosis and prognosis of FCon, thereby offer a promising option in the treatment. The next frontier of FCon research is actively exploring mechanisms of individual risk to improve prevention and treatment approaches.

Independent component analysis (ICA) is a data-driven technique for analyzing resting-state fMRI data by capturing hidden or underlying source signals among the hyper-complex organization of the human brain in resting state to determine components that are maximally statistically independent [20]. ICA can explore the functional architecture of the brain, and its relationship with brain function; it is superior to other methods of fMRI analysis [21]. In the current study, fMRI with ICA was employed to examine FC strength within and functional network connectivity (FNC) [22] between RSNs in 39 female patients with FCon and 36 female HC. Five RSNs, including BGN, SN, left, and right control executive-networks (LCEN/RCEN), and DMN were first identified, and FNC was then used to examine the interactions between these RSNs. We hypothesized that patients with FCon had altered FC within and interactions between RSNs and that alterations would be associated with constipation symptoms.

Materials and methods

Participants

The experiments were conducted in accordance with the Declaration of Helsinki. Female patients with FCon were recruited from a clinical site at the hospital, and female healthy subjects were recruited from the local community. An experienced gastroenterologist diagnosed FCon based on Rome IV criteria [23]. The current study included FCon patients with a variety of major bowel habits including functional defecatory disorders, slow transit constipation, and a combination of the two types. FCon patients with the following symptoms were excluded, including medical/mental/neurological disorders requiring immediate treatment, constipation after childbirth, pelvic floor muscle relaxation/congenital giant colon/redundant sigmoid colon, and current medications that could affect the central nervous system. All subjects received a complete physical exam with history and signed an informed consent form. Thus, 39 female patients with FCon (right-handed, age 37.3 ± 1.7 years) and 36 female healthy controls (right-handed, age 41.8 ± 2.5 years, Table 1) were included in the current study.

All participants were required to complete the state-trait anxiety inventory (STAI) to assess the severity of their anxiety. They were also asked to complete the Patient Assessment of Constipation Symptoms (PAC-SYM) [24] and Patient Assessment of Constipation Quality of Life Scale (PAC-QOL) [25] to assess patients’ constipation symptoms and quality of life.

MRI acquisition

The experiment was carried out using a 1.5 T Signa HDXT (GE, Milwaukee, WI, USA) scanner. Following localizers, a coronal T2-weighted sequence (TR = 4600 ms, TE = 122 ms, matrix size = 256 × 256, field of view = 240 × 240 mm², slice thickness = 6 mm, and slice spacing = 1 mm) was collected
to rule out any cranial organic lesion. For each subject, the sagittal three-dimensional T1-weighted fast spoiled gradient recalled echo (T1-FSPGR) sequence was acquired with the following parameters: TR = 9.1 ms, TE = 3.0 ms, slice thickness = 1 mm and 248 slices, matrix size = 256 × 256, and field-of-view = 512 × 512 mm². Then, gradient echo T2*-weighted echo planar imaging sequence was used to obtain resting-state functional images with the following parameters: TR = 2000 ms, TE = 40 ms, field-of-view = 256 × 256 mm², matrix size = 64 × 64, 29 axial slices, flip angle = 90 degrees, and isotropic resolution of 4 mm³. The scan for resting-state fMRI lasted 400 s and participants were instructed to open their eyes during scanning.

**Image processing**

The fMRI data were preprocessed using Statistical Parametric Mapping 12. The first five time points were removed to ensure magnetization equilibrium; slice-timing and head movement correction were performed. Then, the images were normalized to the Montreal-Neurological-Institute (MNI) template and were then resampled to a field-of-view of 3 × 3 × 3 mm³. Finally, smoothed with an isotropic Gaussian kernel (full-width-at-half-maximum = 6 mm³). In addition, head motion differences among the groups were compared. This analysis was conducted by averaging the frame-wise displacement (FD) from every time point for each participant, and there was no significant group difference in subjects’ motion (P > 0.05) for mean FD calculated from six translation/rotation parameters obtained from the realignment process. For FC analysis, head motion parameters, global signals, white-matter signals, and cerebrospinal fluid were regressed out as nuisance covariates [26]. fMRI time points that were severely affected by motion were removed using a “scrubbing method” (FD value > 0.5 mm, and root mean square variance of blood oxygen level-dependent (BOLD) signal intensity, i.e., DVARS > 0.5% between consecutive time points) [26], and less than 5% of time points were scrubbed for each subject. In the end, high-frequency noise and low-frequency drift were eliminated using a band-pass filter (0.01–0.1 Hz).

**Independent component analysis**

The smoothed fMRI data were analyzed by using the spatial group ICA [27] of the fMRI Toolbox (GIFT) software version 3.0b to identify spatially independent and temporally coherent networks. First, resting-state fMRI data of 39 female patients with FCon and 36 female HC were concatenated by the principal component analysis and 26 principal components were obtained by using a minimum description length approach. Then, the Infomax ICA algorithm was repeated 20 times in ICASSO which is a software for investigating the reliability of ICA estimated by clustering and visualization [28]. Finally, these 26 independent components (ICs) were individually back-reconstructed for each participant. The resulting image maps and time courses were converted into z-scores, calculating the spatial correlation between ICs and templates (Stanford’s Functional Imaging in Neuropsychiatric Disorders Lab; http://findlab.stanford.edu/ functional_ROIs.html). The ICs showing the highest spatial correlation with these RSN templates were selected [29].
FNC analysis

We used the FNC toolbox (TRENDS Center, version 2.3a) to calculate the temporal correlation between five RSNs [22]. The maximal lagged correlation approach with a lag that varied between −3 and 3 s at 3/25-s intervals was conducted to estimate pairwise correlations between the five selected ICs (in a total of 10 combinations). The differences in FNC were tested via a two-sample t-test with STAI as a covariate (Supplementary Methods).

Group difference within RSNs

Among the 26 components, five components were selected as five RSNs, including DMN, BGN, SN, LCEN, and RCEN. For each RSN, a mask was defined by conducting a one-sample t-test of the Z-maps from the two groups. In order to calculate the differences between the two groups, we performed a two-sample t-test (P < 0.05, false wise error-FWE corrected) on the Z-maps of the five RSNs within the corresponding masks.

FC analysis within RSNs with group differences in FNC

The pairwise FC strength consisting of a region×region matrix for each subject was calculated. In order to examine the differences between the two groups, an independent sample t-test was conducted. Within the RSNs which showed group differences in FNC, the regions-of-interest (ROIs) which belong to the key hubs in RSNs were defined by conducting a one-sample t-test of the Z-maps from the two groups. The voxels centered at the MNI coordinate with a peak t score and its surrounding voxels within a radius of 6 mm were selected for further correlation analyses. Thus, a one-sample t-test of the Z-maps from the two groups was performed in these five RSNs, and ROIs (center at the coordinates of the peak value with a 6 mm radius) which represent the key hubs of each RSN were defined correspondingly. For the DMN, ventromedial prefrontal cortex (VMPFC), precuneus (PCUN), and left- and right angular gyri (ANG_L, ANG_R) were selected. For the SN, left- and right insula (INS_L, INS_R) and ACC were selected. Left and right caudate (CAU_L, CAU_R) and left and right thalamus (THA_L, THA_R) were selected in the BGN. Left dorsolateral prefrontal cortex (DLPFC_L) and ANG_L were selected in the LCEN. For the RCEN, right DLPFC (DLPFC_R) and ANG_R were selected. Furthermore, the significance of group differences in pairwise correlations from all ROIs was tested using a two-sample t-test to assess the abnormalities within RSNs between patients with FCon and HC.

Clinical measurement correlation

Pearson correlations were used to calculate the association between imaging data and clinical measurements in patients with FCon. The FNC between the selected RSNs and their correlations with clinical measurements can be acquired. Bonferroni correction was used for multiple comparisons (P < 0.002 (0.05/27)). On the other hand, the FC strengths between ROIs and their correlations with clinical measurements were also conducted. Bonferroni correction was used for multiple comparisons (P < 0.003 (0.05/18)).

Results

Demographic characteristics

There was no significant difference in age between patients with FCon and HC group (P > 0.05, Table 1). SAI and TAI were higher for patients with FCon than for HC (P < 0.001, Bonferroni corrected). PAC-SYM and PAC-QOL scores of the FCon group are also shown in Table 1.

Identification of RSNs

We calculated the spatial correlation between ICs and the anatomical masks of each network to determine which ICs had the strongest spatial correlation with functional networks of interest (DMN, BGN, SN, LCEN, and RCEN). The ICs showing the highest correlation with these RSNs were IC17 (DMN, r = 0.61991), IC5 (BGN, r = 0.31034), IC15 (SN, r = 0.53556), IC22 (LCEN, r = 0.63165), and IC19 (RCEN, r = 0.55784, Supplementary Figure S1).

FNC analysis

One-sample t-tests showed eight connections with positive and significant correlation coefficients in both FCon and HC groups (Fig. 1A). Same orientations of the arrow were observed in both groups (Fig. 1B). Two-sample t-tests revealed that two network connections of SN-BGN (P = 0.0032, t = 3.049) and DMN-LCEN (P = 0.0044, t = 2.938) had a significant stronger FNC in FCon than that in HC (Fig. 1A). The SN-RCEN (P = 0.0049, t = −2.905) connection had a significant stronger FNC in HC than that in FCon (Fig. 1A).

FC analysis within RSNs

Two-sample t-test of FNC showed significant differences in FNC in three connections of the SN-BGN (P = 0.0032, t = 3.049), SN-RCEN (P = 0.0049, t = −2.905), and DMN-LCEN (P = 0.0044, t = 2.938). Two-sample t-test on the
Z-maps of the five RSNs within corresponding masks showed that there was no significant difference between the two groups.

For the BGN-SN, SN-RCEN, and DMN-LCEN connections, the results of the independent sample t-test are shown in Figs. 2 and 3. Within the BGN-SN connection, FCon compared with HC had higher pairwise FC strengths of CAU_L-INS_L, THA_R-INS_L, CAU_R-INS_L, and THA_L-ACC (Fig. 2A, \( P < 0.0024 \) (0.05/21)). Within the SN-RCEN connection, FCon showed lower pairwise FC strengths of INS_L-DLPFC_R and INS_R-DLPFC_R (Fig. 2B, \( P < 0.005 \) (0.05/10)). Within the DMN-LCEN connection, FCon showed higher pairwise FC strengths of VMPFC-ANG_L, PCUN-ANG_L, and VMPFC-DLPFC_L (Fig. 3A, \( P < 0.003 \) (0.05/15)).

**Correlation between imaging data and clinical measurement in FCon**

FNC of the SN-RCEN was negatively correlated with the PAC-QOL total score (\( P = 0.0001, r = -0.5080 \), Fig. 4) and worries/concerns (\( P = 0.0043, r = -0.4475 \)) in FCon. There were positive correlations between FNC of the DMN-LCEN and stool symptoms of the PAC-SYM scale in FCon (\( P = 0.0003, r = 0.5534 \), Fig. 4).

FC strength of the VMPFC-DLPFC was not only positively correlated with worries/concerns of the PAC-QOL scale (\( P = 0.0002, r = 0.5564 \)), but also with the PAC-QOL total score in FCon (\( P = 0.0013, r = 0.4964 \), Fig. 3B). FC strength of PCUN-ANG_L was positively correlated with rectal symptoms of the PAC-SYM scale (\( P = 0.0031, r = 0.4614 \)) and PAC-SYM total score in FCon (\( P = 0.0033, r = 0.4593 \), Fig. 3B).
Discussion

In the current study, we employed resting-state fMRI with ICA to explore alterations in FC within and FNC between five RSNs in patients with FCon. FC analysis within RSNs showed that patients with FCon compared to HC had increased FNC of BGN-SN and DMN-LCEN and reduced FNC of SN-RCEN. Subsequent interaction analysis between RSNs showed that changes in regional FC contributed to abnormal FNC in FCon. Correlation analysis between RSNs and clinical measures revealed that the FNC of SN-RCEN was negatively correlated with worries/concerns and total score of PAC-QOL scale, whereas FNC of the DMN-LCEN was positively correlated with stool symptoms of the PAC-SYM scale. FC strength of VMPFC-DLPFC_L was positively correlated with worries/concerns and the PAC-QOL total score, whereas FC strength of PCUN-ANG_L was positively correlated with rectal symptoms of the PAC-SYM scale and PAC-SYM total score.

Alterations in FNC between BGN and SN

Our data showed significant group differences in three network connections in patients with FCon relative to HC, including increased FNC of BGN-SN, DMN-LCEN, and decreased FNC of SN-RCEN. The SN is a paralimbic network that deals with internal attention, cognition, emotion, and regulation functions [12, 30]. BGN, which consists of four nuclei including the striatum (caudate, putamen, and nucleus accumbens), globus pallidus (internal and external sectors), substantia nigra/ventral tegmental area, and subthalamic nucleus [31], is involved with diversity function including motor control and reward processing [32]. Visceral afferent signals such as abdominal distension/pain reach the primary interoceptive cortex through the thalamus which is the key node of BGN [33], regulating affective, motor, and motivational brain responses to visceral sensation [30]. Enhanced FNC of BGN-SN indicates that the BGN exaggerates the saliency value of abnormal visceral sensation and emotional regulation.
Fig. 3 Two-sample t-test of pairwise FC in DMN-LCEN. The color bar shows the t values. The depth of red and blue color shows the degree of FCon>HC/HC>FCon. The symbol of one asterisk, two asterisks, and three asterisks denotes $P<0.05$, $P<0.01$, and $P<0.001$, respectively. Combined with the t and $P$ value, the darker the blue/red color, the smaller the $P$ value. (A) Two-sample t-test of pairwise FC in DMN-LCEN. (B) Correlation analysis between the pairwise FC of DMN-LCEN connections and clinical measures in patients with FCon. Abbreviation: FC, functional connectivity; DMN, default mode network; LCEN, left control executive network; VMPFC, ventromedial prefrontal cortex; PCUN, precuneus; ANG, angular gyrus; DLPFC, dorsolateral prefrontal cortex; FCon, functional constipation; PAC-QOL, Patient Assessment of Constipation Quality of Life Scale; PAC-SYM, Patient Assessment of Constipation Symptom Scale; HC, healthy controls

Fig. 4 Correlation analysis between FNC strength of RSNs and clinical measures in patients with FCon. Abbreviation: FNC, functional network connectivity; BGN, basal ganglia network; SN, salience network; RCEN, right control executive network; LCEN, left control executive network; FCon, functional constipation; HC, healthy controls; PAC-QOL, Patient Assessment of Constipation Quality of Life Scale
Results showed that increased FC strengths of CAU_L-INS_L, THA_R-INS_L, CAU_R-INS_L, and THA_L-ACC in FCon contributed to increased FNC of BGN-SN. INS and ACC are the key nodes of SN. ACC plays a significant role in emotional response regulation, decision-making, and emotional responses to visceral stimulation [34]. THA receives input from the basal ganglia nucleus and projects it to the prefrontal cortex to regulate cortical activity [35]. The increased FC strength of THA_L-ACC may reflect the enhanced attention, emotional responses, and regulatory resources of visceral afferent signals in patients with FCon [13]. The INS has numerous functions ranging from sensory and emotional processing to advanced cognition [36]. A recent graph-theoretical study found the aberrant nodal topological properties of the INS and THA in patients with FCon, and the nodal degree was associated with the sensation of incomplete evacuation and difficulty of defecation [5]. Our data showed increased FC strength of THA_R-INS_L, indicating the FCon-related abnormality in these two regions and their relationship, though we did not obtain significant correlation with constipation symptoms. CAU-associated functional/structural abnormalities have been reported in pain processing in patients with IBS [37, 38]; patients with FCon also showed abdominal distention/pain and difficulty in defecation which is related to visceral discomfort; thus, increased FC strength of CAU_L-INS_L and CAU_R-INS_L revealed abnormal crosstalk between visceral sensation and pain processing.

Alterations in FNC between SN and RCEN

The nervous system is continuously bombarded by internal and external stimuli. A leading priority is to identify the most homeostatically relevant among these myriads of inputs. This capacity requires a system that can integrate highly processed sensory data with visceral and autonomic signals [39], so that the organism can decide what it should do next. SN is supposed to be well suited for this purpose. CEN is equipped to operate on identified salience which requires directing attention to pertinent stimuli as behavioral choices are weighed against shifting conditions, background homeostatic demands, and context. To achieve this level of response flexibility, the brain must exert control over posterior sensorimotor representations and maintain relevant data in mind until actions are selected [12]. Our data showed that reduced FNC of SN-RCEN was associated with higher worries/concerns, which indicated the dysfunction of RCEN in regulating the salience of negative visceral sensation detected by SN, resulting in sustained excessive attention to visceral stimulation and finally negative emotions including anxiety and depressive status.

The large-scale connectivity of the INS positions plays a critical role in triaging and integrating internal and external multisensory stimuli in the service of initiating higher-order control functions, as well as serving as a critical gatekeeper to executive control [40]. DLPFC (sustained attention), ventrolateral prefrontal cortex (response suppression), and amygdala have an impact on regulating the visceral response via emotions such as anxiety and stress [41]. Our data showed that reduced FC strengths of INS_L-DLPFC_R and INS_R-DLPFC_R in patients with FCon reflect the dysfunction of the DLPFC in shifting attention from negative visceral sensations [41, 42].

Alterations in FNC between DMN and LCEN

DMN is involved in self-referential processing, including monitoring emotional state and physical condition [43], and altered DMN connectivity has also been revealed in patients with IBS [44]. One study reported that FC of the INS and cingulate seeds both increased significantly in patients with IBS in the VMPFC, dorsomedial prefrontal cortex, and posterior cingulate cortex, revealing excessive coupling of the SN with CEN and DMN [16]. Increased FNC of DMN-LCEN was associated with higher score stool symptoms of the PAC-SYM scale in patients with FCon, indicating that the constipation symptoms were monitored by the DMN, which was different from the healthy status by attracting excessive attention and enhancing the interaction between the DMN and LCEN.

PCUN is the key hub of the DMN, which is related to the processing of self-referential information [45]. As a part of the DMN, the VMPFC is related to disturbed emotion regulation [46]. The higher FC of the VMPFC-DLPFC was related to higher negative emotion scores, indicating reduced capacity of the DLPFC in regulating VMPFC function to process negative emotions. Previous study revealed the connectivity of PCUN and ANG was strongly related to the efficiency of conducting executive control attention performance [47]. The aberrant FC of PCUN and ANG_L was positively correlated with rectal symptoms of the PAC-SYM scale, suggesting that more attention has been paid to the bowel movement in patients with FCon as a consequence of negative emotions, which would worsen constipation symptoms.

Limitations

The 1.5 T scanner used in the present study has a relatively lower signal-to-noise ratio and functional contrast-to-noise ratios when compared to a 3 T scanner. Only female subjects were included in this study, and male patients could be included in future studies to fully understand the intrinsic network deficits related to functional constipation. We explored the relationship between RSNs including BGN, DMN, SN, LCEN, RCEN, and more RSNs, which can be considered for a more comprehensive analysis.
Conclusion

The current study investigated alterations in FC and FNC within and between RSNs in patients with FCon compared with HC. Results revealed that patients with FCon had increased interactions of the BGN-SN and DMN-LCEN and reduced interactions between SN and RCEN compared with HC. FNC analysis suggested that aberrant RSN interactions in patients might be associated with abnormalities in emotion regulation and constipation symptoms. Changes in regional FC within different networks may be related to abnormal FNC among RSNS. In FCon patients, increased FNC of the DMN-LCEN was associated with stool syndromes, and reduced FNC of the SN-RCEN was associated with worries/concerns and the PAC-QOL total score. Changes in regional FNC among RSNs. In FCon patients, increased FNC of the DMN-LCEN was associated with stool syndromes, and reduced FNC of the SN-RCEN was associated with worries/concerns and with rectal symptoms, respectively. The findings provided evidence that patients with FCon had altered FC within and interactions between RSNS, which were associated with constipation symptoms.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10072-022-06275-6.

Declarations

Ethics approval The experimental protocol was approved by the Institutional Review Board of Xijing Hospital and was registered in the Chinese Clinical Trial Registry Center as: ChiCTR-OOB-15006347 (http://www.chictr.org.cn). The experiments were conducted in accordance with the Declaration of Helsinki.

Conflict of interest None

Informed consent Written informed consent was obtained from all participants.

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