Female Urology, Urodynamics, Incontinence, and Pelvic Floor Reconstructive Surgery

Abnormal Brain Functional Connectivity Strength in the Overactive Bladder Syndrome: A Resting-State fMRI Study

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OBJECTIVE	To investigate the whole-brain functional connectivity strength (FCS) of patients with the overactive bladder syndrome (OAB).
METHODS	This study investigates the changes of intrinsic whole brain functional connectivity pattern in OAB using FCS. We acquired resting-state fMRI data from 26 OAB patients and 28 healthy controls. FCS was used to compute the long-range and short-range FCS values for each voxel in the brain of each subject. The long or short-range FCS maps were compared between OAB patients and healthy controls. Pearson's correlation coefficients was also performed between abnormal FCS regions and clinical/psychometric scores in patients.
RESULTS	Compared with healthy control subjects, the OAB patients exhibited significantly decreased short-range FCS in the right medial superior frontal gyrus and bilateral anterior cingulate gyrus, and increased short-range FCS in the middle frontal gyrus, the precentral gyrus, and bilateral caudate nucleus. In addition, significantly decreased long-range FCS was found in bilateral middle cingulate gyrus and posterior cingulate gyrus. Furthermore, the abnormal FCS values in the right caudate nucleus showed significantly negative correlation with Self-Rating Depression Scale of OAB patients.
CONCLUSION	Patients with OAB have abnormal short-range and long-range FCS in brain regions associated with brain-bladder network. Our study provides new insights into the underlying brain network topology of OAB. UROLOGY 131: 64−70, 2019. © 2019 Elsevier Inc.

Overactive bladder (OAB) represents a syndrome characterized by a myriad of lower urinary tract symptoms including urinary urgency, with or without urge incontinence, usually with frequency and nocturia, in the absence of infection or other identifiable causes.[1] OAB is highly prevalent, and the symptoms associated with this condition can significantly affect the social, psychological, occupational, domestic, physical, and sexual aspects of life for those who suffer from it.[2] Contemporary studies suggest that decreased inhibition by the central nervous system with affective factors might

be associated with OAB. Specifically, it is reported that OAB patients show symptoms of anxiety or depression.[3]

Results from functional magnetic resonance imaging (fMRI) have shown that neural control of the bladder involves many different regions of the brain, such as the anterior cingulate gyrus, the prefrontal gyrus, the insula, the basal ganglia, and cerebellum, leading to the new concept of a brain-bladder control network.[4] These brain regions are regulated by multiple factors, such as the filling of the bladder, the safety of voiding, and emotional and social propriety.[5] Changes in the supraspinal network are suggested to be a possible contributing factor in such OAB. In addition, the beneficial effects of behavioral treatments improving on bladder symptoms suggest that the central nervous system is a major causative factor.[6]

Previous fMRI studies of OAB patients have mainly depended on task-based fMRI. In contrast to task-based fMRI, resting-state fMRI requires no stimulation or response and detects intrinsic neuronal activity with increased resolution and reliability.[7,8] Thus, resting-state fMRI is an effective platform for exploring neuronal functional architecture via connectivity analyses and understanding the pathophysiological mechanisms of intrinsic

activity in OAB patients. Functional connectivity (FC) refers to the neurophysiological relationship between anatomically separated brain regions. The value of the FC is the correlation coefficient of the time-signal points between 2 brain regions.[9,10] The graph−based FC strength (FCS) represents the summation of the relationships between a given voxel and all other voxels in the brain. The neurological mechanism of FCS has been revealed; the process is closely related to regional cerebral blood flow and glucose metabolism.[11] As a data-driven approach, FCS was designed for a large-scale, bias-free, and prior-hypothesis-free whole brain network analysis. In addition, this computational approach allows differentiation between local and distant connectivity (ie, short-range and long-range FCS) across the brain on the basis of their anatomical distance.

To the best of our knowledge, this study is the first to employ FCS metrics to investigate the FC of OAB patients. We hypothesized that OAB patients would show abnormal functional hubs and connections in brain regions associated with the bladder-brain control network. The current study aims to identify the abnormalities of brain network topology in OAB patients using FCS mapping and to investigate the association between abnormal FCS values and neuropsychological performance.

PATIENTS AND METHODS

Subjects and Questionnaires
This prospective study was approved by the Committee for Human Research at ***Hospital (disclosure of hospital name/other identifier during review process) and followed by all regulations (2015-ke-21), and all participants provided informed consent. Twenty-six subjects with OAB and 28 healthy control participants were included in this study. For a diagnosis of OAB, patients must complain of urinary urgency, with or without urge incontinence, usually with frequency and nocturia, in the absence of infection or other identifiable causes, in accordance with the 2002 ICS (International Continence Society) definition. Controls must have no prior diagnosis of OAB or interstitial cystitis/bladder pain syndrome, no significant lower urinary tract symptoms (American Urological Association symptom index <7), no bladder or pelvic pain, and no evidence of urinary infection. The inclusion criteria were as follows: (1) ≥18 years old, (2) diagnosed with OAB, and (3) willing to participate in the study and capable of understanding the study procedures and questions. The exclusion criteria were the following: (1) new-onset or chronic neurological disorders (such as stroke, spinal cord damage, Parkinson's disease, and multiple sclerosis), (2) urinary tract infections within the last month of the survey, (3) a postvoid residual volume ≥150 mL and/or pelvic organ prolapse, (4) history of bladder surgery, and (5) urethral obstruction (eg benign prostate hyperplasia). OAB symptoms were assessed using a version of the OAB symptom score (OABSS),[12] developed for and validated in the Japanese population. OAB was divided into 3 groups according to the following score ranges: mild, a total score ≤5; moderate, a total score of 6-11; severe, a total score ≥12. To assess the cognitive function of OAB patients in this study, we used the Mini-Mental State Examination as an objective test. To quantify the severity of anxiety or depression

symptoms in OAB patients, we administered the Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) before the MRI scans.

MRI Data Acquisition
The subjects emptied their bladders before undergoing MRI. All MRI data were acquired on a 3.0-T MR system (MAGNETOM Prisma, Siemens, Erlangen, Germany) with a standard 64-channel head coil receiver at the Magnetic Resonance Center of ***Hospital (disclosure of hospital name/other identifier during review process). A standard birdcage head coil and foam padding were used to limit head motion and diminish scanner noise. A high resolution T1-weighted anatomical image was obtained prior to the functional scan (repetition time = 1900 ms; echo time = 2.52 ms; slices = 176; flip angle = 9°; field of view = 256 mm × 256 mm; data matrix = 256 × 256; in-plane resolution = 1 mm × 1 mm). Resting-state functional images were acquired with a gradient-echo planar imaging sequence using the following settings: repetition time = 2000 ms; echo time = 30 ms; slices = 33; flip angle = 90°; field of view = 224 mm × 224 mm; in-plane matrix resolution = 64 × 64; in-plane resolution = 3.5 mm × 3.5 mm. During the scan, subjects were required to lie in the scanner with their eyes closed, to stay awake, and to refrain from thinking systematically about anything.

Image Preprocessing and FCS Analysis
The resting-state image data were analyzed using Data Processing and Analysis of Brain Imaging software (http://rfmri.org/dpabi),[13] which is based on Statistical Parametric Mapping (http://www.fil.ion.ucl.ac.uk/spm). For each participant, the first 10 images were discarded to ensure steady-state longitudinal magnetization. The functional images were slice-timing corrected and realigned for head motion correction. Subjects with head motion of any volume more than 2 mm of maximum displacement in the x-, y-, or z-axis, and 2° of angular motion were excluded from further processing. Registered images were spatially normalized to Montreal Neurological Institute space (resampling voxel size = 3 × 3 × 3 mm^3). The resulting time series in each voxel was then linearly detrended and bandpass filtered (0.01-0.08 Hz) to extract the low-frequency oscillations. Nuisance signals representing motion parameters, white matter, and cerebrospinal fluid signals were regressed out to control the potential impact of physiological artifacts. Here, we used the Friston 24-parameter model to regress out head motion effects.

Whole-brain connectivity was analyzed by a graph theory approach: voxel-based FCS (eg weighted degree centrality), which was further divided into short-range and long-range FCS. Pearson's correlation coefficients were computed between the time series of all pairs of gray matter (GM) voxels within the GM mask, and a whole-brain FC matrix was obtained for each participant. Individual correlation matrices were then transformed into a z-score matrix using Fisher z-transformation to improve normality.[14] The FCS metric is derived from the degree centrality of a weighted network in graph theory. In brief, for a given voxel i, its FCS can be derived using the following equation

$$FCS(i) = \sum_{j=1, \ j\neq i}^{N} z_{ij}, \ r_{ij} > r_0$$

where N is the number of voxels; z_{ij} is the correlation coefficient after Fisher's Z-transformation, r_{ij}, between voxel i and voxel j; and r_0 is a threshold used to eliminate weak correlations possibly arising from noise (generally, $r_0 = 0.25$). This procedure was limited to a

conjunct template of a GM mask, which was generated by thresholding (cutoff = 0.25) the mean map of all GM maps involving all subjects. The short-range FCS of a voxel was defined as the FCS with anatomical distances less than a specified threshold, whereas the long-range FCS was defined as the distances greater than the threshold. We obtained short- and long-range FCS according to the widely accepted cutoff point of 75 mm. The images were then smoothed with a Gaussian kernel of a 4-mm full-width half maximum Gaussian Kernel for the statistical analysis.

Statistical Analysis
The normality of fMRI data distributions was checked by the Lilliefors goodness-of-fit test in the REST Normality Test.[15]

Within-Group FCS Analysis
To explore the within-group short- or long-range patterns, we performed 1-sample t tests on the individual FCS maps in a voxel wise way for each group. The resulting statistical map was performed for multiple comparisons using Gaussian random field theory (uncorrected voxel $P<.001$, corrected cluster $P<.05$). The results were visualized with BrainNet Viewer (http://www.nitrc.org/projects/bnv/).

Between-Group FCS Analysis
Two-sample t tests were performed to investigate the between-group differences of short- or long-range FCS at each voxel within a GM mask. Age and gender were imported as covariates in the 2-sample t test statistical analysis to avoid any confounding effects. To eliminate the effect of structural differences on results, we also entered the GM volume maps resulting from segmentation as covariates in the functional data analysis. The resulting statistical map was performed for multiple comparisons using Gaussian random field theory (uncorrected voxel $P<.001$, corrected cluster $P<.05$).

Correlation Analysis
To investigate the association between abnormal short- or long-range FCS values and clinical indices, we separately selected brain regions with significant intergroup differences in short- or long-range connectivity to create spherical ROIs (r = 6 mm) centering at the point of peak t value. Then, the mean FCS values were extracted from these regions and correlated with the SAS, SDS, and OABSS scores, respectively. A threshold of $P<.05$ was considered statistically significant.

RESULTS

Demographic Data and Clinical Comparisons
Demographics and clinical data of both OAB patients and healthy controls are listed in Table 1. No significant difference in gender, age, or education level was found between patients and control subjects ($P>.05$). OABSS scores were used to define and classify OAB as mild (n = 4), moderate (n = 16), or severe (n = 6). All subjects had normal Mini-Mental State Examination scores, while SAS and SDS scores were significantly higher in patients than in controls.

FCS Results
The result of the Lilliefors goodness-of-fit test demonstrated that data were in accordance with the normal distribution (The Supplementary Fig. 1). The 2 groups exhibited similar spatial distributions of both long-range and short-range FCS. Furthermore, the 1-sample t test results showed the topography of the cortical hubs with strong FCS. The stronger long-range FCS mainly distributed in the bilateral posterior cingulate gyrus (PCG)/precuneus, temporal cortex, inferior parietal lobule (IPL), and dorsolateral prefrontal cortex. The stronger short-range FCS was preferentially distributed in the bilateral PCG/precuneus, anterior cingulate gyrus (ACG), posterior parietal cortex, occipital lobes, precentral gyrus (PreCG), and prefrontal cortex (Fig. 1).

Two-sample t test results revealed differences in the FCS maps between the 2 groups. Compared to healthy controls, the OAB patients exhibited significantly decreased short-range FCS in the right medial superior frontal gyrus (SFGmed. R) and left ACG (ACG. L), and increased short-range FCS in the middle frontal gyrus (MFG. R), the PreCG. R, and the bilateral caudate nucleus (CAU). In addition, OAB patients showed significantly decreased long-range FCS in the bilateral middle cingulate gyrus (MCG) and PCG (Fig. 2 and Supplementary Table 1).

Correlation Analysis
As shown in Fig. 3, a negative correlation was found between SDS scores and short-range FCS values in the CAU. R (r = −0.5243, $P= .0060$).

DISCUSSION
The current study demonstrates that OAB patients have abnormal FCS in the brain-bladder control network, mainly located in the SFGmed, ACG, MFG, PreCG, CAU, MCG, and PCG. In addition, the FCS of the CAU.R is related to the clinical characteristics of OAB patients. These brain regions are considered to be involved in the conscious and social control of bladder function. To the best of our knowledge, this study is the first to apply FCS to explore the short-range and long-range FC of OAB patients.

The control of continence is an example of motivational control of executive function.[16] Many studies have

Table 1. Demographic and clinical data in patients with OAB and healthy control group

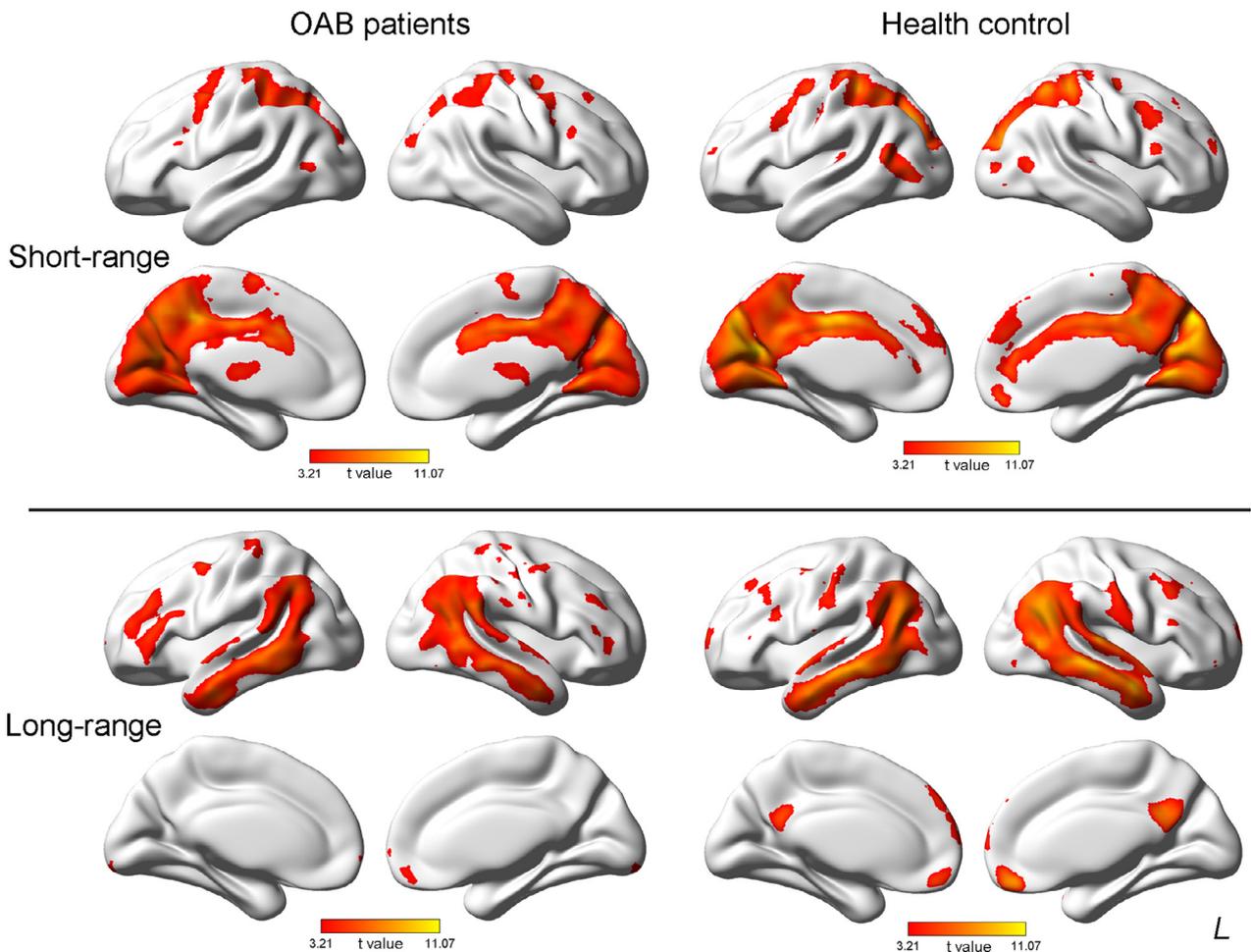|	OAB (n = 26)	Control Group (n = 28)	P Value
Sex (male/female)	23/3	26/2	NA
Age (years)	43.58 ± 13.42	50.12 ± 12.11	$P = .0654$
Handedness (right/left)	26/0	28/0	NA
Levels of education (years)	12.27 ± 4.74	14.02 ± 2.37	$P = .0887$
MMSE	28.42 ± 1.31	29.23 ± 1.78	$P = .0640$
OABSS	8.43 ± 2.83	NA	NA
SAS	45.82 ± 1.78	39.48 ± 1.30	$P = .0047$
SDS	53.61 ± 1.78	43.15 ± 1.50	$P = .0001$

Figure 1. Representative 1-sample *t* test results of FCS values in OAB patients and healthy controls (*P*<.05, GRF corrected). L, left. Colorscale denotes *t* values. (Color version available online.)

reported mPFC alterations in OAB patient. The mPFC is activated in the urine-withholding phase,[4] and the SFGmed is part of the mPFC. A possible interpretation of our results is that decreased FCS of the SFGmed results in inhibition of urine holding and promotes the voiding reflex in the context of the OAB.

Activity in the cingulate gyrus has been linked with both visceral pain and nonpainful visceral stimulation.[17] The urge to void is regarded as a type of nonpainful visceral stimulation and decreases the activity of the cingulate gyrus. In our study, we found decreased short-range FCS of the ACG. Previous studies have revealed that the ACG is relevant to micturition control, including the sensation of bladder fullness, micturition control, and pelvic floor contractions.[18] We are the first to report that the MCG and the PCG exhibit decreased long-range FCS in patients with OAB. In line with our findings, earlier studies have found that stimulation of a posterior part of the cingulate gyrus in cat interrupts micturition when the bladder is filled rapidly.[19] A task-based fMRI study reported that the PCG showed hyperactivity in patients with self-reported urinary incontinence and that activity in the PCG correlated positively with daytime incontinence frequency.[20] Our study

finds increased long-range FCS of the PCG, serving as a proof-of-concept that the PCG is an important hub in the regulation of micturition. From another perspective, the cingulate cortex is responsible for integrating the emotional context with interoception.[21] Similar abnormalities of interoceptive network activation are observed in patients with fibromyalgia and irritable bowel syndrome, diseases sometimes termed as "hypervigilant" states.

The MFG is an important hub of the central executive network (CEN),[22] which is engaged in decision making. On the other hand, the default-mode network (DMN), is active in the resting state and deactivated when conscious attention to a cognitive task is required. It is assumed that a full bladder demands increased attention, resulting in deactivation of the DMN. The anticorrelation means that when 1 network is activated, the other is deactivated during rest (eg the DMN and the CEN).[23] In our study, we found increased FCS in MFG, a CEN hub, and decreased FCS in hubs of the DMN (eg the PCG and the dMPFC). Previous studies have shown that brain networks affected by such interventions, such as the DMN and CEN, are associated with improved behavioral outcomes and cognitive performances.[24] Thus, we hypothesize that cognitive
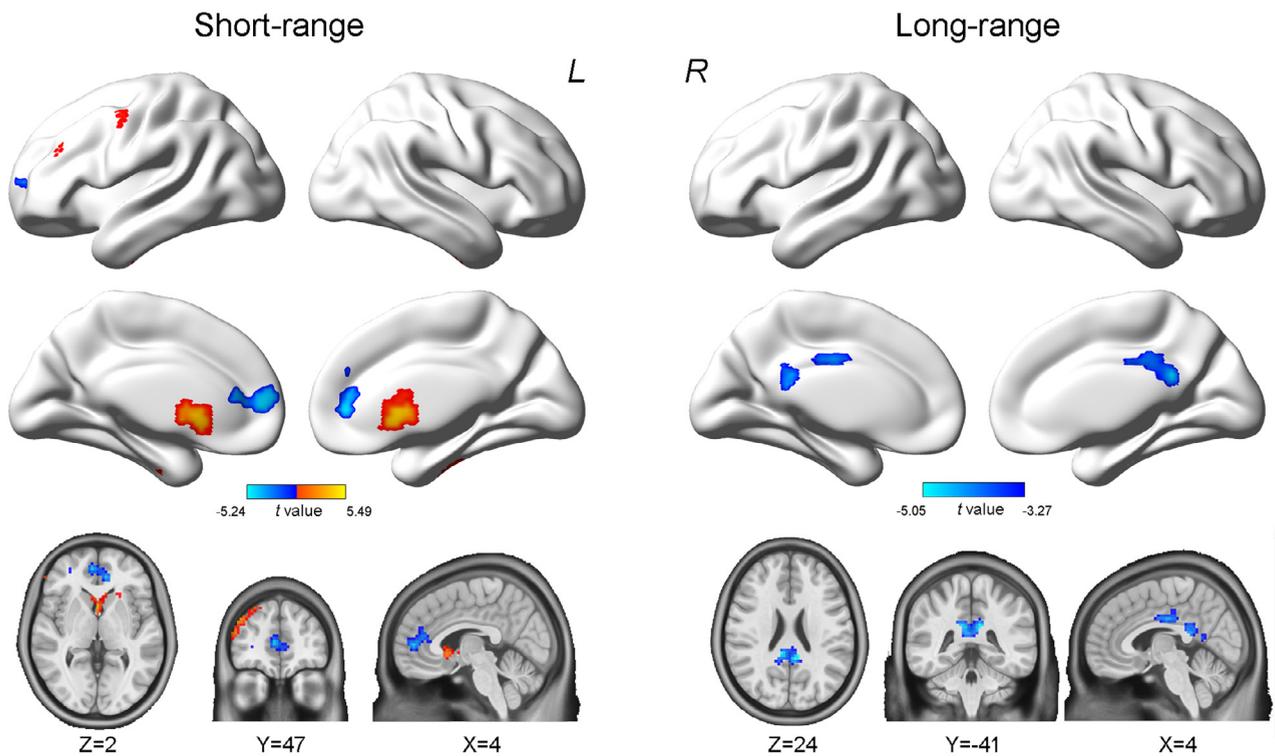
Short-range

Long-range

Figure 2. FCS differences between OAB patients and healthy controls (P<.05, GRF corrected). Compared with healthy subjects, individuals with OAB showed significantly decreased short-range FCS in the SFGmed. R and ACG. L (cold colors); increased short-range FCS in the MFG. R, PreCG.R, and bilateral CAU (warm colors); and decreased long-range FCS in the bilateral MCG and PCG (cold colors). Colorscale denotes the *t* value. X, Y, Z, MNI coordinates. ACG. L, left anterior cingulate gyrus; CAU, caudate nucleus; L, left; MCG, middle cingulate gyrus; MFG. R, right middle frontal gyrus; PCG, posterior cingulate gyrus; PreCG.R, right precentral gyrus; R, right; SFGmed. R, right medial superior frontal gyrus. (Color version available online.)
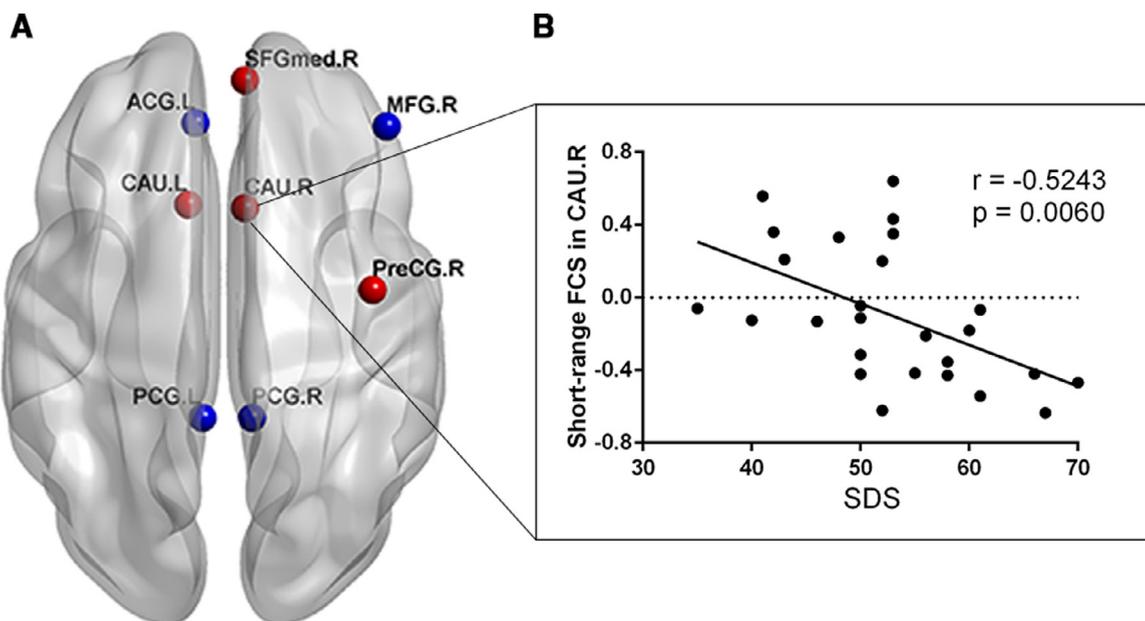

Figure 3. Pearson correlation between significantly abnormal FCS and clinical data. SDS scores negatively correlate with short-range FCS values for the CAU.R (r = −0.5243, P= .0060). CAU, caudate nucleus; FCS, functional connectivity strength; SDS, Self-Rating Depression Scale. (Color version available online.)

or physical training may improve the clinical symptoms of OAB patients.

Response inhibition is an executive function that allows the detection and modification of unwanted actions. The PreCG is mainly involved in planning and executing movements. The precentral gyrus showed activity during a response inhibition task.[25] In the current study, the increased short-range FCS of PreCG in OAB patients may be compensatory activity related to impaired response inhibition of the brain-bladder control network.

The CAU, originally thought to primarily be involved in the control of voluntary movement, is now also known to be an important part of cognitive and behavioral functions. Event-related analyses of functional MR imaging data have indicated a significant increase in CAU/putamen involvement during the self-initiated condition.[26] Moreover, findings of another study of healthy females confirmed that initiation of micturition was associated with activation of the CAU.[27] Growing evidence indicates that depressive condition is associated with abnormal neural reward circuitry including the CAU.[28] The CAU is activated most strongly during the receipt of reward. Considerable evidence indicates that reward processing is dysfunctional in individuals with major depressive disorder. Previous studies have suggested that OAB could be an important cause of emotional disorders, including anxiety and depression.[29] In our study, the SDS scores of the patients are significantly higher than those of the control subjects and there were negative correlations between SDS scores and short-range FCS values in the CAU. Recently, a meta-analysis also reported that OAB was associated with increased rates of depression and/or anxiety symptoms.[30] This association may be assumed that the social impact of OAB reduces the functional capacity of the individual and generates stress leading to anxiety and depression. The co-occurrence may also indicate that urinary and affective symptoms share common biological pathways. However, the exact nature of the association of OAB with anxiety and depression remains unknown.

Some limitations of our study should be noted. First, the patient sample enrolled in our cohort is relatively small; further study in a large sample is required to strengthen the statistical findings and arrive at a general conclusion. Second, comparison of the long-range and short-range FCS values did not reveal significant differences among the 3 subgroups (mild (n = 4), moderate (n = 16), and severe (n = 6)). We will continue to expand the sample size to compare the FCS of OAB patients with different levels of severity. Third, our study is a cross-sectional study. Long-term follow-up after clinical intervention can be performed in future studies to reveal the correlation between OAB symptoms and FCS alteration.

CONCLUSION

Our resting-state FC analysis found extensive FCS abnormalities in key brain regions involved in the bladder-brain network. Aberrant intrinsic organization and interconnectivity of the FCS are characteristics of OAB patients.

Understanding these mechanisms may offer a route to the treatment of OAB in patients without overt neurological disease. Behavioral treatments of OAB based on fMRI may provide new insights into clinical practice.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.05.019.

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