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# Sacral Neuromodulation Improves Abnormal Prefrontal Brain Activity in Patients with Overactive Bladder: A Possible Central Mechanism

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*Full-length article available at auajournals.org/10.1097/JU.0000000000002445.*

**Study Needs and Importance:** The incidence of overactive bladder (OAB) is high and seriously affects quality of life, but its pathogenesis is still unclear. Sacral neuromodulation (SNM) can improve the symptoms of refractory OAB. However, the mechanism of action of SNM is unclear. It is of great significance to explore the central pathogenesis of OAB and the central action mechanism of SNM, which may promote the emergence of new treatments for OAB.

**What We Found:** A total of 16 healthy control (HC) and 20 OAB patients were enrolled. SNM treatment was successful in 18 OAB patients and failed in 2, and all OAB patients were reevaluated postoperatively. The assessment method we used was prefrontal cortex functional near-infrared spectroscopy scan synchronous urodynamic monitoring. We found abnormal deactivation of the left dorsolateral prefrontal cortex (DLPFC: channel 7) in OAB patients (part *a* of figure), which may be the central pathogenesis of OAB. A possible central mechanism of SNM for OAB is to restore activation of the left DLPFC (parts *b* and *c* of figure). Compared with the SNM success group, the failure group showed abnormal deactivation of left DLPFC, suggesting that a greater degree of deactivation of the left DLPFC may be associated with a poorer response to SNM.

**Limitations:** One limitation of this study is that functional near-infrared spectroscopy can only reach the cerebral cortex with limited detection depth, resulting in changes in the activation of the deep brain nucleus that cannot be measured. Another limitation is the small sample size of the failure group, which we will expand in the future.

**Interpretation for Patient Care:** This is the first prospective HC study to explore the central mechanism of SNM during SNM start-up. Our study provides novel neuroimaging evidence for the possible central pathogenesis of OAB and the possible central mechanism of SNM.

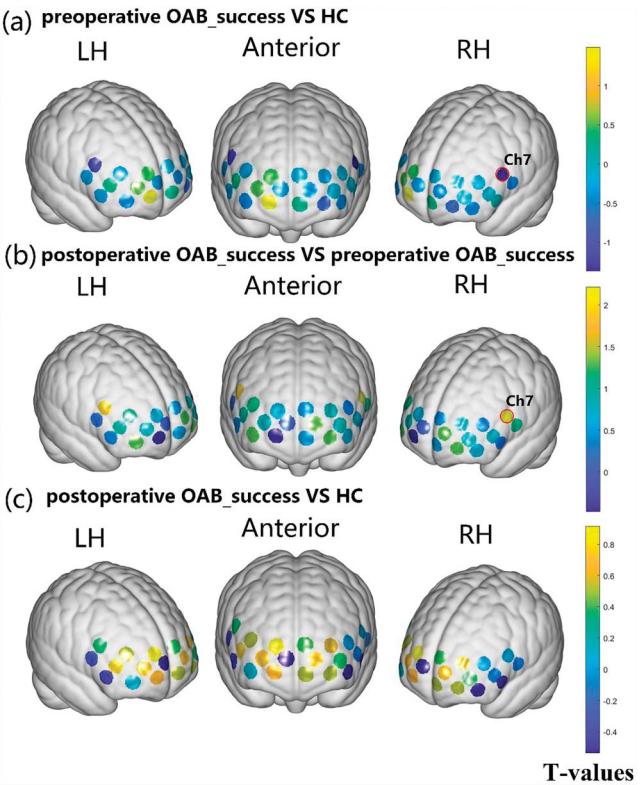


**Figure.** Prefrontal activation changes between the pre- and postoperative OAB_success and HC groups. *a*, compared with HC group, activation of the preoperative OAB_success. *b*, compared with the preoperative OAB_success group, activation of the postoperative OAB_success. *c*, compared with the HC group, activation of the postoperative OAB_success. Each dot represents a channel. Channels marked with red circles indicate significant differences in activation ($p < 0.05$, false discovery rate corrected). The color bar represents the T values at the group level. The warm color denotes activation, and the cold color denotes deactivation. *LH*, left hemisphere. *RH*, right hemisphere.

THE JOURNAL OF UROLOGY®


https://doi.org/10.1097/JU.0000000000002445
Vol. 207, 1256-1267, June 2022
Printed in U.S.A.

THE JOURNAL of UROLOGY®
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# Sacral Neuromodulation Improves Abnormal Prefrontal Brain Activity in Patients with Overactive Bladder: A Possible Central Mechanism

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**Purpose:** We explored the central pathogenesis of overactive bladder (OAB) and the central mechanism of action of sacral neuromodulation (SNM).

**Materials and Methods:** We prospectively enrolled patients with OAB who chose SNM and healthy controls (HCs). At baseline, all subjects completed a 72-hour voiding diary, OAB symptom score and prefrontal cortex functional near-infrared spectroscopy scan synchronous urodynamic monitoring. All OAB patients were tested after implantation of the SNM electrode, and both success and failure groups were reevaluated. NIRS_KIT software was used to analyze prefrontal activity ($p < 0.05$ and corrected by false discovery rate). SPSS® 22.0 was used to analyze clinical parameters, and $p < 0.05$ was considered statistically significant.

**Results:** A total of 16 HC and 20 OAB patients were enrolled. SNM treatment was successful in 18 OAB patients and failed in 2. The parameters of the voiding diary, OAB symptom score and urodynamic monitoring of OAB group were significantly improved after SNM treatment in success group, not in the failure group. Compared with HCs, Brodmann's area 9 (left dorsolateral prefrontal cortex [DLPFC]) was significantly deactivated in the preoperative OAB success group and significantly activated after SNM treatment. Before surgery, compared with the success group, the failure group showed significantly deactivated Brodmann's area 9 (left DLPFC).

**Conclusions:** Our study provides novel neuroimaging evidence for the possible central pathogenesis of OAB (ie abnormal deactivation of the left DLPFC) and the possible central mechanism of action of SNM (ie restore activation of the left DLPFC).

**Key Words:** spectroscopy, near-infrared; brain mapping; urination; urodynamics

**Abbreviations and Acronyms**

BA = Brodmann's area
CBF = cerebral blood flow
Ch = channel
DLPFC = dorsolateral prefrontal cortex
DMPFC = dorsal medial prefrontal cortex
DO = detrusor overactivity
fNIRS = functional near-infrared spectroscopy
FSF = first sensation of filling
fMRI = functional magnetic resonance imaging
FDR = false discovery rate
HC = healthy control
MCC = maximum cystometric capacity
MNI = Montreal Neurological Institute
OAB = overactive bladder
OABSS = overactive bladder symptom score
PAG = periaqueductal gray
Pdet = detrusor pressure
PFC = prefrontal cortex
PVR = post-void residual volume
SNM = sacral neuromodulation
UUI = urgency urinary incontinence

OVERACTIVE bladder (OAB) is a syndrome defined by urinary urgency, usually with frequency and nocturia, with or without urgency urinary incontinence (UUI), in the absence of urinary tract infection or other obvious pathology.[1] The prevalence of OAB is high, about 16% to 43%,[2,3] seriously affecting patient quality of life, but its pathogenesis is still unclear, which

Accepted for publication January 11, 2022.
Support: The study was supported by the National Natural Science Foundation of China (No. 82170792).
Conflict of Interest: none declared.
Ethics Statement: Study received approval by the Ethics Committee of China Rehabilitation Research Center (IRB 2020-040-1).
Clinical trial No. ChiCTR1900025473.
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https://doi.org/10.1097/JU.0000000000002445
Vol. 207, 1256-1267, June 2022
Printed in U.S.A.

undoubtedly increases the difficulty of OAB treatment. Sacral neuromodulation (SNM) can improve the symptoms of refractory patients in whom OAB does not respond to first-line therapies, including behavioral and/or drug therapy.[4] However, the mechanism of action of SNM in treating OAB is unclear. Previous studies have suggested that the possible mechanisms include inhibiting detrusor overactivity (DO) without affecting urethral resistance during urination,[5] inhibiting the C fiber and sympathetic neuron activity to avoid DO,[6] and regulating the spinal cord reflex and brain networks by peripheral afferents.[7]

In addition, 1 positron emission tomography study[8] and 2 functional magnetic resonance imaging (fMRI) studies[9,10] found that SNM altered activity in several brain regions associated with bladder control in OAB patients, including prefrontal cortex (PFC), cingulate gyrus, insula and periaqueductal gray (PAG), providing important insight into the central mechanisms of action of SNM. However, they were all cross-sectional studies, and without healthy control (HC) group, which could not differentiate the extent of the change in brain activity from other factors, nor could they evaluate whether the brain activity after SNM treatment was consistent with that of healthy people. Moreover, the SNM devices in fMRI scanners may have potential hazards (eg movement, dislocation, lead heating and damage),[11] so the manufacturer only approved magnetic resonance imaging scans with a 1.5 T magnet for patients with SNM implants while the device is turned off,[10] which may result in the loss of real-time brain response information during SNM stimulation. The functional near-infrared spectroscopy (fNIRS) is a noninvasive option-based functional brain imaging technique with high temporal resolution[12,13] and no interference with the operation of SNM, making it a good choice to study the central mechanism of action of SNM.

We prospectively enrolled OAB and HC groups and performed simultaneous urodynamic monitoring with fNIRS scans during SNM stimulation, which may provide more comprehensive, reliable, and real-time information for exploring the central mechanism of SNM in OAB patients.

## MATERIALS AND METHODS

### Subjects

After approval by the Ethics Committee of China Rehabilitation Research Center (IRB 2020-040-1), we recruited 20 patients (10 women; mean±SD age 49.05±16 years) with refractory idiopathic OAB who chose SNM and 16 HC with sex and age matching (12 females; mean±SD age 40.69±15.19 years), all of whom signed informed consent. Patients diagnosed with OAB according to the criteria of the International Continence Society,[1] with symptoms lasting for at least 3 months, were treated with SNM after failure of at least 2 anticholinergic medications or an anticholinergic drug and beta-3 agonist. Exclusion criteria included other causes of lower urinary tract symptoms (eg urinary tract infections, bladder stones or tumors, benign prostatic hyperplasia, neurological diseases), history of SNM surgery, history of botulinum toxin injections within 1 year, bladder pain syndrome, urinary retention (post-void residual volume >150 ml), pregnancy and cognitive impairment. Inclusion criteria for HC were normal voiding diary, OAB symptom score (OABSS) and urodynamic results. Exclusion criteria included neurological and urinary diseases, other major systemic diseases, pregnancy and bladder dysfunction caused by oral medication.

### Experimental Procedure

All assessments were not done during menstruation. At baseline, all subjects completed a 72-hour voiding diary, OABSS and PFC fNIRS scan synchronous urodynamic monitoring. Subsequently, OAB patients received an electrode lead from the SNM system (InterStim® II) along the third sacral nerve root using standardized surgical techniques guided by x-ray fluoroscopy.[14] SNM treatment was considered successful if one of the voiding diary parameters (ie mean frequency of urination per 24 hours, mean urine volume, mean frequency of urinary urgency per 24 hours and mean frequency of urinary incontinence per 24 hours) improved at least 50% after 2 to 4 weeks of testing; otherwise, it was considered a failure. At this time, all OAB patients were reevaluated and compared with the preoperative and HC groups. The specific process of fNIRS scan synchronous urodynamic monitoring is as follows (fig. 1). 1) Urodynamic tests in the study were performed in accordance with International Continence Society standards.[15,16] Subjects were asked to lie supine on the examination bed after urination, and we used a catheter to extract the residual urine. A double-lumen 7Fr catheter (to monitor intravesical pressure and infuse and withdraw water) and a single-lumen 10Fr rectal catheter (to monitor abdominal pressure) were inserted into the urethra and rectum and connected with the urodynamic instrument; 2) subjects kept their eyes closed and were fitted with fNIRS electrodes on their forehead, and the lights in the rooms were dimmed; 3) normal saline at 37C was infused into the bladder at a rate of 30 ml per minute, and the first sensation of filling (FSF) was recorded. When the subjects had a strong desire to void (a persistent desire to void without fear of leakage), whether or not the urodynamic monitoring showed DO, the perfusion was stopped, and the maximum cystometric capacity (MCC) was recorded. We used the visual analog scale (0 to 10) to assess the urge to void.[17] After 30 ml were extracted from the bladder with a syringe, the repeated bladder infusion/withdrawal task began, which lasted 7 minutes and 5 seconds, consisting of 5 blocks of 5 stages (rest, 20 seconds; infusion, 30 ml for 20 seconds; pause, 5 seconds; withdrawal, 30 ml for 20 seconds; rest, 20 seconds). The block design task has obvious advantages in reducing unnecessary data fluctuations and human interference.[18] During the task, the fNIRS data of the PFC were collected.

### fNIRS Equipment

fNIRS equipment details were reported in our previous article (see supplementary methods, https://www.jurology.com).[19] The probes were spaced 3 cm apart with the lowest probe row along the Fp1-Fp2 line of the international 10-20

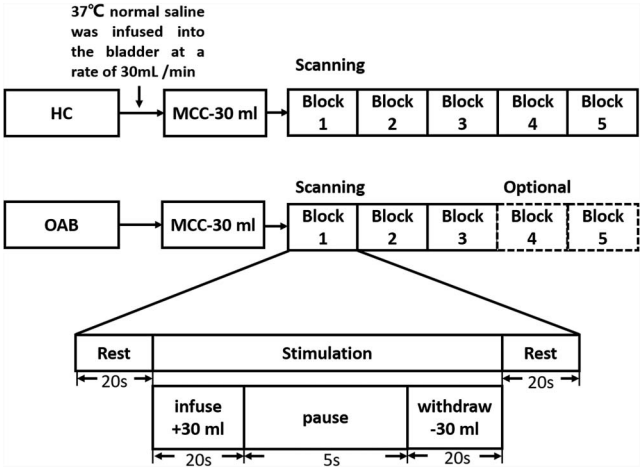


**Figure 1.** Process of fNIRS scan synchronizes urodynamic monitoring. *s*, seconds.

system (fig. 2).[20] The functional transcranial brain atlas was used to obtain the position of all channels (Chs), including the Montreal Neurological Institute (MNI) coordinates and the probability of associated brain regions in the Brodmann's areas (BAs) atlas (table 1).[21]

### fNIRS Data Analysis

A MATLAB toolbox (NIRS_KIT [http://www.nitrc.org/projects/nirskit/])[22] was used to perform fNIRS data preprocessing, analysis, and visualization of the results (see supplementary methods, https://www.jurology.com).

## RESULTS

A total of 16 HC and 20 OAB patients were enrolled. SNM treatment was successful in 18 OAB patients and failed in 2, and all OAB patients were reevaluated postoperatively.

### Comparison of Demographic and Clinical Characteristics between HC and OAB Groups

There were no significant differences in age, gender composition, years of education, handedness, and score of strong desire to void between the OAB and HC groups ($p > 0.05$). The parameters of 72-hour voiding diary (mean frequency of urination per 24 hours, mean frequency of urinary urgency per 24 hours and mean frequency of urinary incontinence per 24 hours) and OABSS in preoperative OAB group were significantly higher than those in HC group, and these indicators were significantly reduced after SNM treatment in the success group, the differences were statistically significant ($p < 0.05$). On the contrary, the mean urine volume, FSF and MCC of preoperative OAB group were significantly lower than those of HC group, and were significantly increased after SNM treatment in the success group, the differences were statistically

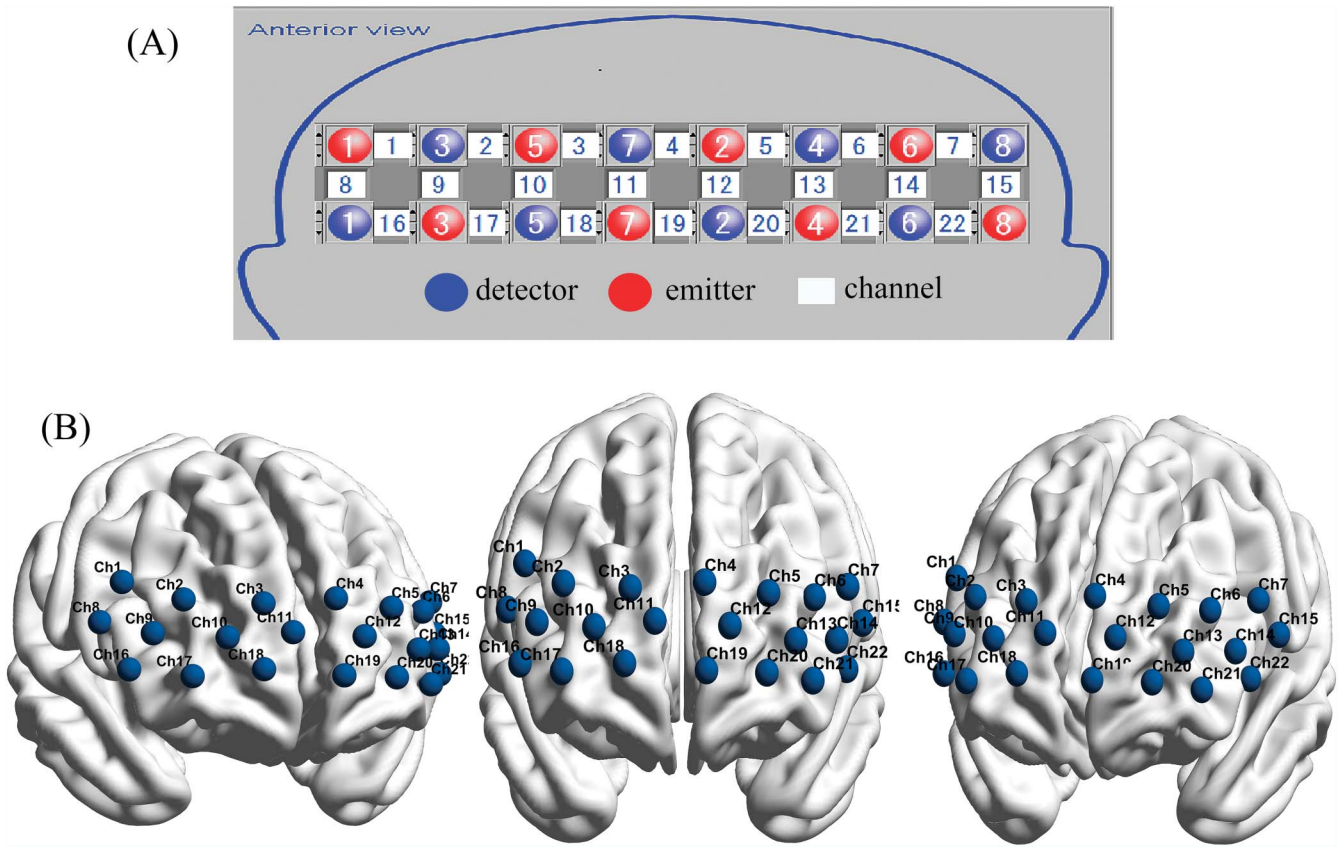


**Figure 2.** The 2*8 arrays probe set (*A*) and 3D MNI coordinates of the 22 Chs (*B*).

**Table 1.** *Ch locations for fNIRS cap*

| Ch | MNI Coordinates (x, y, z) | BA | Brain Area | Probability |
|---|---|---|---|---|
| 1 | 53.09, 26.74, 31.37 | 9 | Rt | 0.79 |
| 2 | 40.07, 49.89, 25.65 | 9 | Rt DLPFC | 0.79 |
| 3 | 17.52, 64.27, 24.36 | 9 | Rt DMPFC | 0.79 |
| 4 | −7.64, 64.47, 25.98 | 9 | Lt DMPFC | 0.79 |
| 5 | −29.25, 58.22, 22.92 | 9 | Lt DLPFC | 0.79 |
| 6 | −44.66, 45.28, 21.7 | 46 | Lt DLPFC | 0.61 |
| 7 | −55.98, 21.56, 24.68 | 9 | Lt DLPFC | 0.79 |
| 8 | 58.95, 21.87, 18.21 | 9 | Rt DLPFC | 0.79 |
| 9 | 49.02, 45.16, 14.6 | 46 | Rt DLPFC | 0.61 |
| 10 | 29.74, 63.63, 13.27 | 10 | Rt frontopolar area | 0.92 |
| 11 | 9.2, 69.72, 14.97 | 10 | Rt frontopolar area | 0.92 |
| 12 | −16.19, 68.4, 13.62 | 10 | Lt frontopolar area | 0.92 |
| 13 | −38.43, 58.91, 9.29 | 10 | Lt frontopolar area | 0.92 |
| 14 | −52.28, 39.05, 9.49 | 46 | Lt DLPFC | 0.61 |
| 15 | −60.88, 11.92, 14.38 | 44 | Lt pars opercularis Broca's area | 0.73 |
| 16 | 54.72, 38.15, 2.77 | 46 | Rt DLPFC | 0.61 |
| 17 | 40.63, 60.05, 0.58 | 10 | Rt frontopolar area | 0.92 |
| 18 | 19.42, 70.09, 2.84 | 10 | Rt frontopolar area | 0.92 |
| 19 | −8.28, 70.72, 0.82 | 10 | Lt frontopolar area | 0.92 |
| 20 | −28.68, 64.9, 0.19 | 10 | Lt frontopolar area | 0.92 |
| 21 | −44.19, 54.77, −2.08 | 10 | Lt frontopolar area | 0.92 |
| 22 | −55.62, 31.67, 1.2 | 45 | Lt pars triangularis of inferior frontal gyrus | 0.7 |

significant ($p < 0.01$). The specific results of the success group are shown in table 2. Nine patients in the successful OAB group had DO, which improved significantly after SNM treatment ($p < 0.01$). Detrusor pressure (Pdet) was stable in the remaining 9 OAB patients and HC group during filling, and there was no significant difference between them. In contrast, the 2 patients in the failed OAB group showed DO with no improvement after treatment.

## Comparison of fNIRS Data between HC and OAB Groups in "Strong Desire to Void" State

The brain areas showing significant activation changes involved in each group (ie HC, preoperative OAB_success, postoperative OAB_success, preoperative OAB_failure and postoperative OAB_failure) are outlined in detail in table 3. In short, compared with HC, the BA 9 (left dorsolateral PFC [DLPFC]: Ch7) was significantly deactivated in the preoperative OAB_success group and significantly activated after SNM treatment. Moreover, there was no significant difference in PFC activation between the postoperative OAB_success and HC groups, as shown in figures 3 and 4. However, compared with HC, the BA 9 (bilateral DLPFC: Ch1 and Ch7) was significantly deactivated in the preoperative OAB_failure group. Before surgery, compared with the success group, the failure group showed significantly deactivated BA 9 (left

**Table 2.** *Comparison of demographic and clinical characteristics of HC and success group*

| | HC | Preop OAB | Postop OAB | p Value (HC vs preop OAB) | p Value (preop vs postop OAB) |
|---|---|---|---|---|---|
| Total No. | 16 | 18 | 18 | | |
| Mean yrs age (SD) | 40.69 (15.19) | 49.22 (16.35) | 49.22 (16.35) | 0.126 | |
| No. gender (%): | | | | 0.134 | |
| Male | 4 (25) | 9 (50) | 9 (50) | | |
| Female | 12 (75) | 9 (50) | 9 (50) | | |
| Mean yrs education (SD) | 10.50 (3.14) | 11.06 (3.04) | 11.06 (3.04) | 0.604 | |
| Handedness | Rt—handed | Rt—handed | Rt—handed | | |
| 72-Hr voiding diary: | | | | | |
| Median frequency of urination/24 hrs (range) | 6 (5—7) | 14.17 (5.33—123.67) | 8.33 (5—21) | <0.001 | <0.001 |
| Mean ml urine vol (SD) | 370.31 (39.73) | 129.30 (76.34) | 200.03 (77.62) | <0.001 | <0.001 |
| Median frequency of urinary incontinence/24 hrs (range) | 0 (0—0) | 0 (0—5.33) | 0 (0—2) | 0.006 | 0.027 |
| Median frequency of urinary urgency/24 hrs (range) | 0 (0—0) | 8 (4—123) | 4 (1—20) | <0.001 | <0.001 |
| Median OABSS (range) | 0 (0—0) | 10 (1—12) | 6 (2—10) | <0.001 | <0.001 |
| Post-void residual (ml) | <10 | <10 | <10 | | |
| Urodynamic monitoring: | | | | | |
| Mean ml FSF (SD) | 211.38 (43.69) | 128.50 (63.78) | 155.44 (59.99) | <0.001 | 0.002 |
| Mean ml MCC (SD) | 429.88 (74) | 235.89 (96.25) | 274.56 (89.61) | <0.001 | 0.006 |
| Median cm $H_2O$ max Pdet during DO (range) | | 32 (17—95)* | 18 (2—88)* | | 0.008 |
| Mean cm $H_2O$ Pdet at end of filling (SD) | 2.19 (1.47) | 4 (2.6)† | 2.89 (2.09)† | 0.081 | 0.179 |
| Mean score of strong desire to void (SD) | 7.75 (0.86) | 8.22 (0.73) | 7.94 (0.73) | 0.093 | 0.056 |

* Data of the 9 OAB patients with DO.
† Data of the 9 OAB patients without DO.

DLPFC: Ch7), and the PFC activation was still significantly different from HC after SNM treatment (figs. 5 and 6).

## DISCUSSION

This is the first prospective study with HCs using neuroimaging to investigate the SNM central mechanism. The SNM devices in fMRI scanners may have potential hazards.[11] Therefore, we took full advantage of fNIRS scanning, which does not interfere with SNM startup operation and provided critical real-time information about brain activity changes during stimulation. In addition, simultaneous urodynamic monitoring during fNIRS scans allowed us to obtain real-time bladder volume and Pdet, which comprised important information.

We found that the BA 9, 46 (right DLPFC), and 45 (left pars triangularis of inferior frontal gyrus) were significantly activated, and BA 9 (left dorsal medial PFC [DMPFC]) was significantly deactivated in the HC group when the desire to void was strong ($p < 0.05$, FDR corrected). Activation/deactivation of the frontal cortex indicates an increase/decrease in oxyhemoglobin concentration/cerebral blood flow (CBF). Consistent with our results, a fNIRS study found that the bilateral DLPFC of healthy adults was significantly activated in the strong desire to void state, indicating that bilateral DLPFC plays an important role in bladder control. The study also found that the stronger the desire to void, the stronger the activation of bilateral DLPFC, which suggests that DLPFC may be related to the perception of bladder sensation.[23] We found that compared with HC, the BA 9 (left DLPFC) of the OAB group was significantly deactivated in the OAB group ($p < 0.05$, FDR corrected). Similar to our results, another fNIRS study found that the bilateral DLPFC were activated in HC groups during bladder filling and that the activation of DLPFC in the OAB group was weaker than that in HC group.[24] We also found significant deactivation of the left DMPFC, which is consistent with previous studies.[25,26] Griffiths et al proposed a simple working model of brain-bladder control after reviewing previous studies. The normal continence mechanism is that the bladder afferent signals is transmitted from PAG through the thalamus to the insula, where the desire to void is encoded and registered. The signals activate DLPFC where the bladder sensation is sensed and urination decisions can be made according to social etiquette. If urination is inappropriate, the medial PFC will be deactivated by its inhibitory connection to the DLPFC, which may increase threshold levels or decrease PAG activity to suppress the voiding reflex.[27] We suggest that the deactivation of DLPFC in OAB patients may lead to decreased inhibition of medial PFC, ultimately leading to the release of inhibition of the voiding reflex, resulting in typical OAB symptoms such as urinary frequency, urgency or UUI.

Here, we sought to explore what was happening in the brain of OAB patients in the success group during stimulation. We found that the BA 9 (left DLPFC) was significantly activated compared with that before surgery, suggesting that SNM significantly increased CBF of the left DLPFC in OAB patients. Consistent with our findings, Blok et al found in a positron emission tomography study that chronic SNM significantly increased CBF in DLPFC in patients with UUI.[8] They suggested that SNM may affect brain regions involved in DO, bladder filling perception, the urge to void and the timing of urination. However, contrary to our and Blok's results, Weissbart et al found significant deactivation

**Table 3.** *Comparison of fNIRS data of the HC, the successful OAB and the failed OAB groups in the "strong desire to void" state*

| Group | Shown in Figure No. | Brain Areas Showing Significant Changes in Activation ($p < 0.05$, FDR corrected) | Activated/ Deactivated |
|---|---|---|---|
| HC | 3, *a* | BA 9, 46 (rt DLPFC [Ch 8 and Ch 16]) | Activated |
| | | BA 45 (lt pars triangularis of inferior frontal gyrus: Ch 22) | Activated |
| | | BA 9 (lt DMPFC: Ch 4) | Deactivated |
| OAB (success): | | | |
| Preop OAB_success | 3, *b* | BA 9 (lt DMPFC: Ch 4 and lt DLPFC: Ch 7) | Deactivated |
| | | BA 10 (lt frontopolar area: Ch 20) | Deactivated |
| Postop OAB_success | 3, *c* | BA 9, 46 (rt DLPFC [Ch 1 and Ch 9]) | Activated |
| Preop OAB_success vs HC | 4, *a* | BA 9 (lt DLPFC: Ch 7) | Deactivated |
| Postop OAB_success vs preop OAB_success | 4, *b* | BA 9 (lt DLPFC: Ch 7) | Activated |
| Postop OAB_success vs HC | 4, *c* | No significant difference | None |
| OAB (failure): | | | |
| Preop OAB_failure | 5, *a* | No significant difference | None |
| Preop OAB_failure vs preop OAB_success | 5, *b* | BA 9 (lt DLPFC: Ch 7) | Deactivated |
| Postop OAB_failure | 5, *c* | BA 9 (rt DMPFC: Ch 3) | Activated |
| Preop OAB_failure vs HC | 6, *a* | BA 9 (bilat DLPFC: Ch 1 and Ch 7) | Deactivated |
| Postop OAB_failure vs preop OAB_failure | 6, *b* | BA 10 (lt frontopolar area: Ch 12) | Activated |
| Postop OAB_failure vs HC | 6, *c* | BA 9 (rt DLPFC: Ch 2) | Activated |
| | | BA 10 (rt frontopolar area: Ch 10) | Activated |

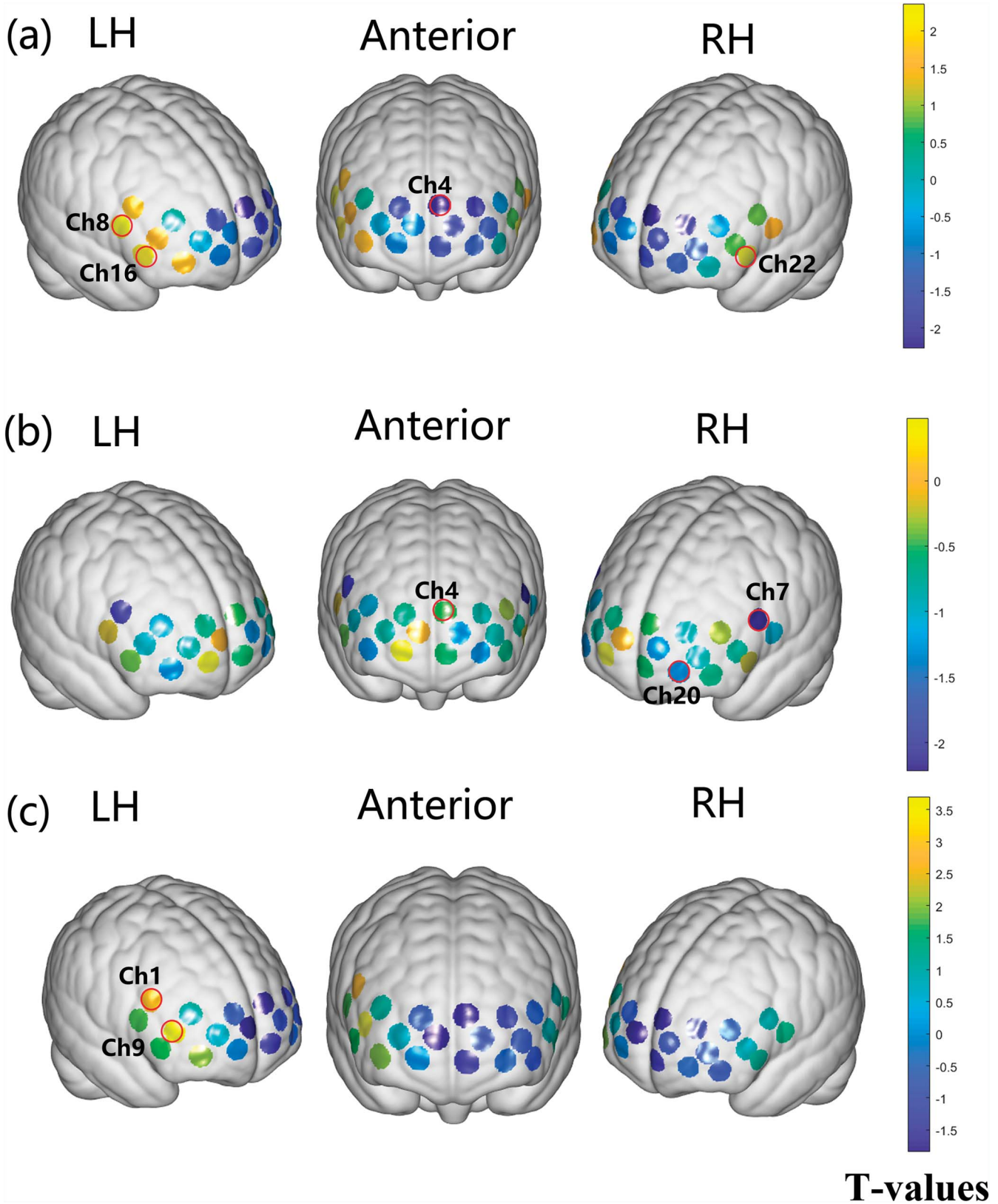


**Figure 3.** Prefrontal activation changes of the HC and OAB_success groups before and after SNM treatment in the "strong desire to void" state. *a*, activation of the HC group. *b*, activation of the preoperative OAB_success group. *c*, activation of the postoperative OAB_success group. Each dot represents a Ch. Chs marked with red circles indicate significant differences in activation ($p < 0.05$, FDR corrected). The color bar represents the T values at the group level. The warm color denotes activation, and the cold color denotes deactivation. *LH*, left hemisphere. *RH*, right hemisphere.

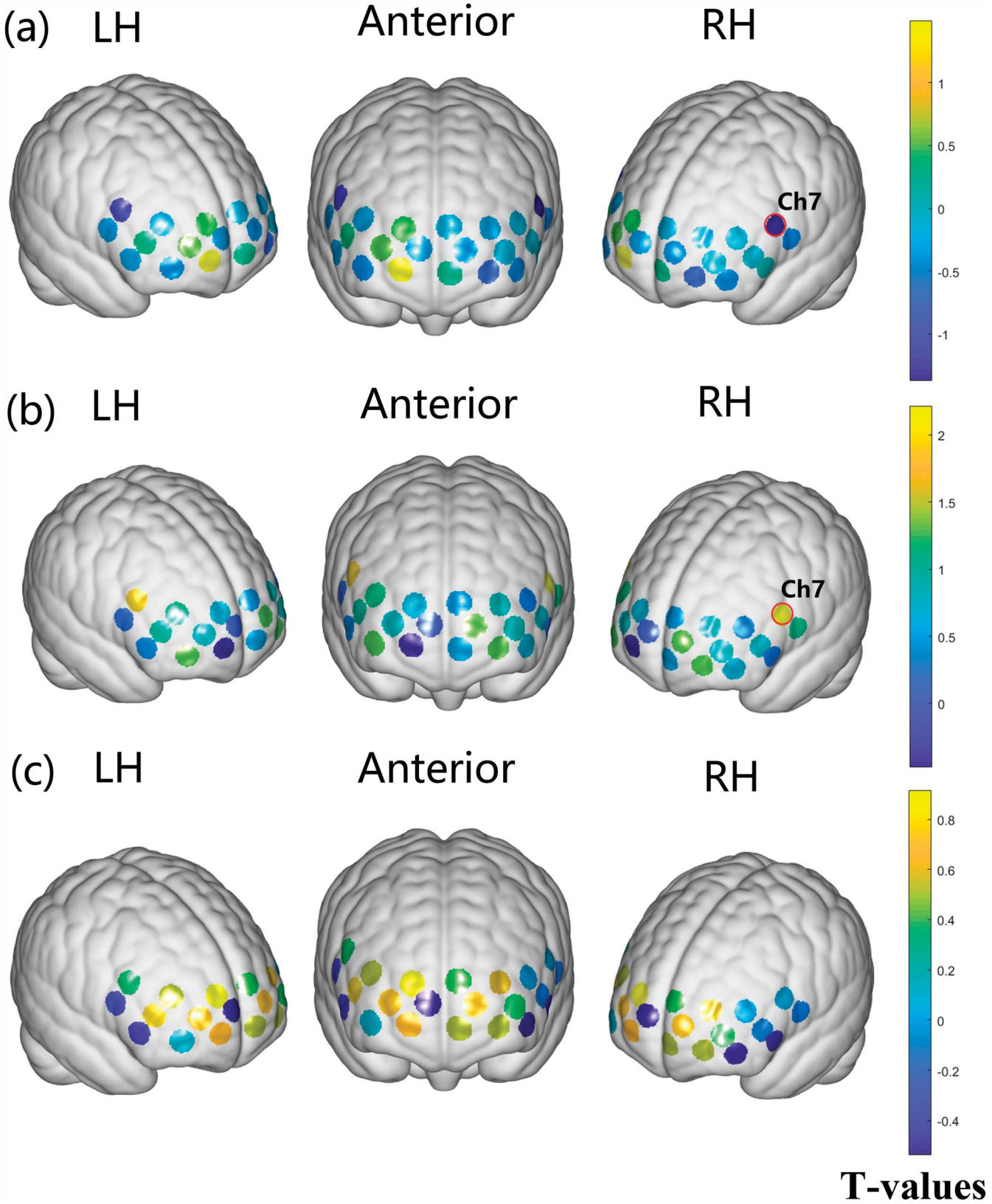


**Figure 4.** Prefrontal activation changes between the pre- and postoperative OAB_success and HC groups. *a*, compared with HC group, activation of the preoperative OAB_success. *b*, compared with the preoperative OAB_success group, activation of the postoperative OAB_success. *c*, compared with HC group, activation of the postoperative OAB_success. Each dot represents a Ch. Chs marked with red circles indicate significant differences in activation ($p < 0.05$, FDR corrected). The color bar represents the T values at the group level. The warm color denotes activation, and the cold color denotes deactivation. *LH*, left hemisphere. *RH*, right hemisphere.

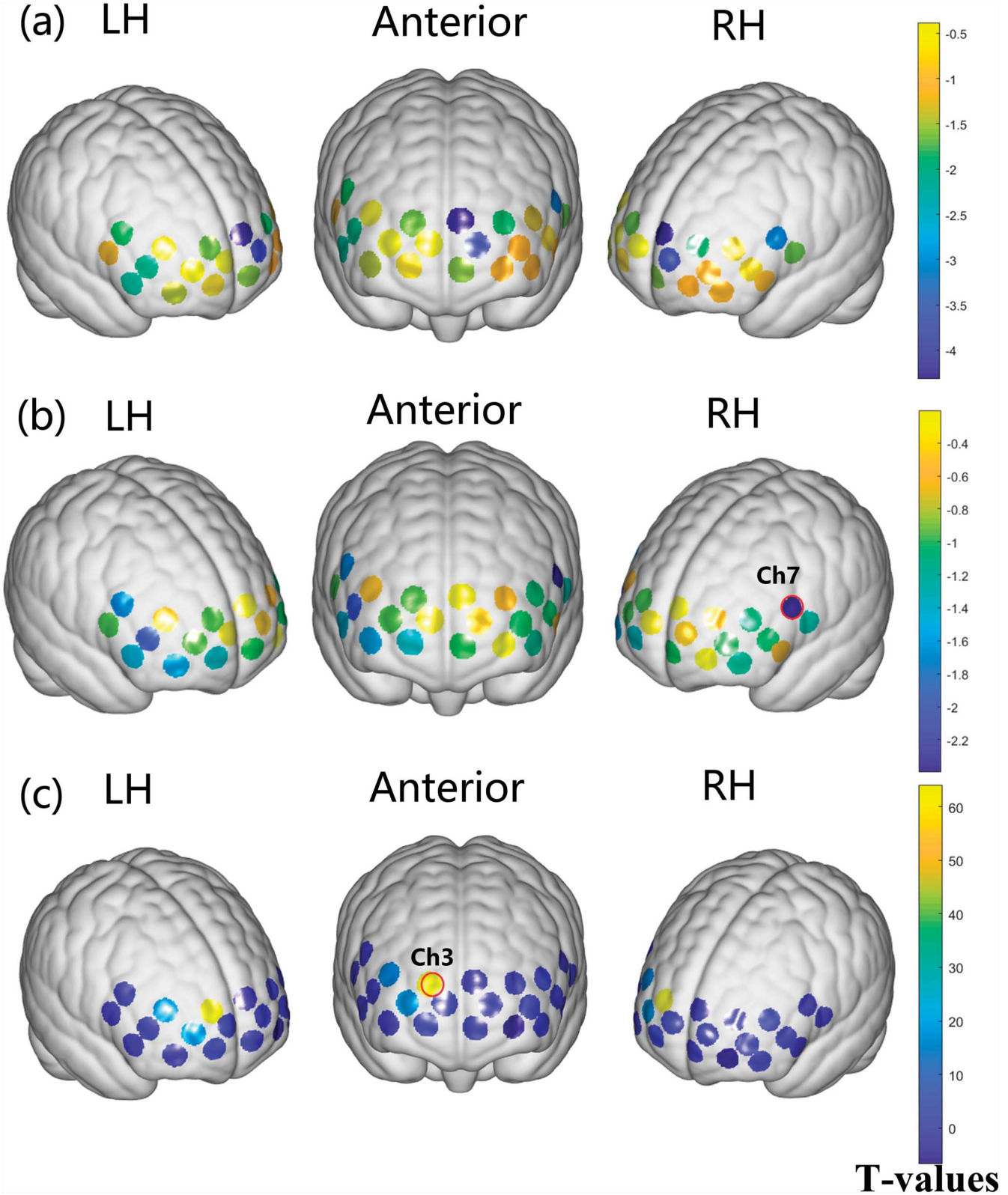


**Figure 5.** Prefrontal activation changes of the OAB_failure group before and after SNM treatment in the "strong desire to void" state. *a*, activation of the preoperative OAB_failure group. *b*, compared with the preoperative OAB_success group, activation of the preoperative OAB_failure. *c*, activation of the postoperative OAB_failure group. Each dot represents a Ch. Chs marked with red circles indicate significant differences in activation ($p < 0.05$, FDR corrected). The color bar represents the T values at the group level. The warm color denotes activation, and the cold color denotes deactivation. *LH*, left hemisphere. *RH*, right hemisphere.

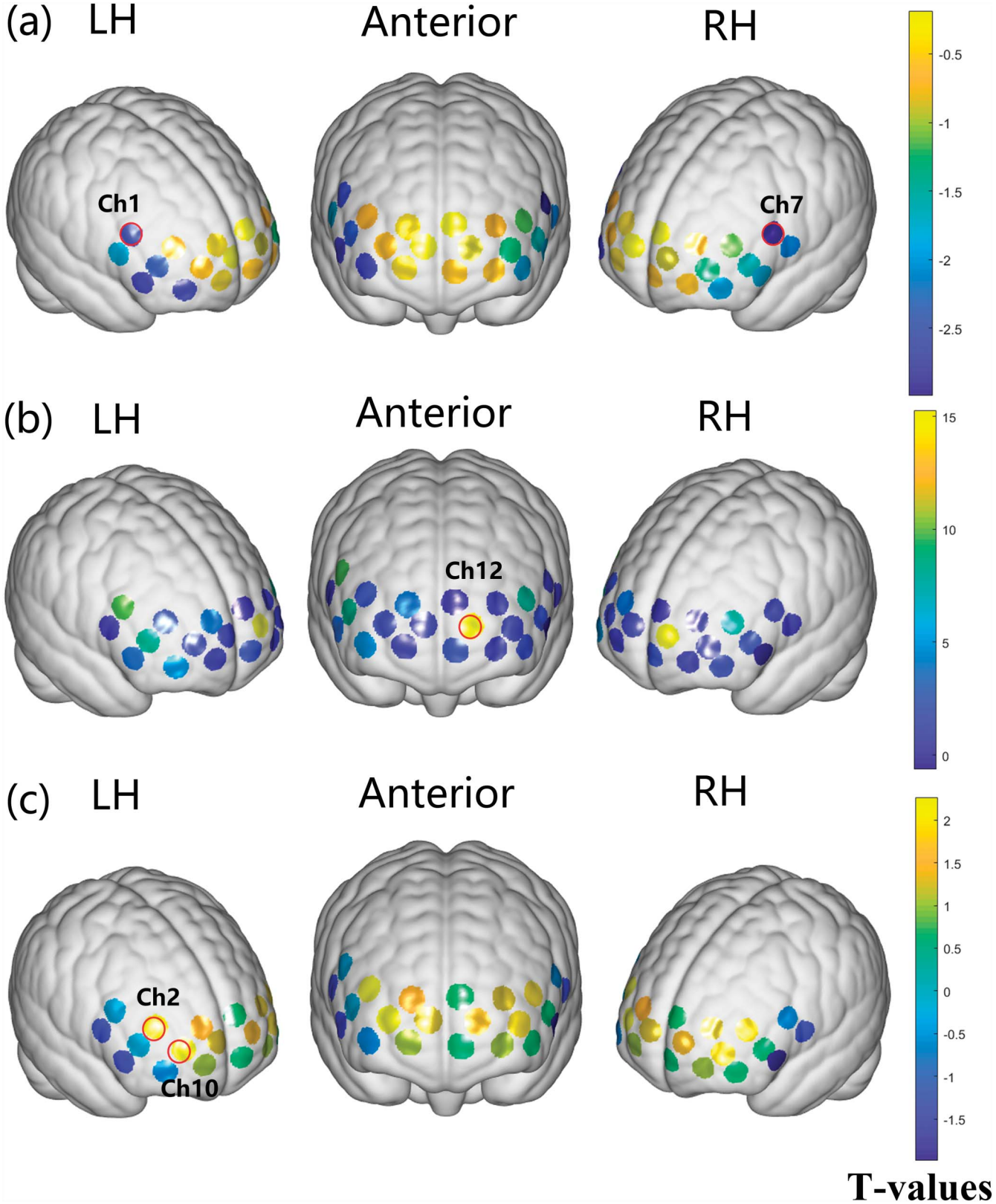


**Figure 6.** Prefrontal activation changes between the pre- and postoperative OAB_failure and HC groups. *a*, compared with HC group, activation of the preoperative OAB_failure. *b*, compared with the preoperative OAB__failure group, activation of the postoperative OAB__failure. *c*, compared with HC group, activation of the postoperative OAB__failure. Each dot represents a Ch. Chs marked with red circles indicate significant differences in activation ($p < 0.05$, FDR corrected). The color bar represents the T values at the group level. The warm color denotes activation, and the cold color denotes deactivation. *LH*, left hemisphere. *RH*, right hemisphere.

of bilateral DLPFC in OAB patients after SNM treatment, which may be related to their SNM being turned off during fMRI scanning,[10] while our and Blok's studies kept SNM switched on. Another fMRI study showed that changes of brain activity varied with SNM stimulus intensity, suggesting that SNM may be involved in downstream regulation of voiding reflex by modulating the activation of medial PFC and lateral PFC.[9] Unfortunately, they all did not include a HC group and could not judge the difference in brain activity between HC and OAB groups. In our study, we found no significant difference in prefrontal brain activity between the OAB and HC groups after SNM treatment, suggesting that SNM may restore the brain activity of OAB patients to near-normal levels and that central nervous system plasticity in OAB patients may also be the mechanism of action of SNM.

In this study, the parameters of a 72-hour voiding diary, FSF and MCC of the preoperative OAB group improved significantly after SNM treatment. At the same time, the DLPFC, which senses bladder sensation was significantly activated in the postoperative OAB group. We suggest that the central mechanism of action of SNM is to correct abnormal bladder afferent signals by regulating ascending sensory nerve impulses. Moreover, the maximum Pdet during DO in the preoperative OAB group was significantly reduced after SNM treatment, consistent with the previous study,[5] suggesting that SNM can also improve lower urinary tract symptoms by inhibiting DO. We think it is likely that the activation of DLPFC inhibits DO by inhibiting the neural circuits mentioned by Griffiths et al.[27]

We also found that the BA 9 (left DLPFC) in the failed OAB group was significantly deactivated before surgery compared with the success group, which is consistent with the result of Weissbart et al.[10] We further compared the postoperative failure group with HC and found that they were still significantly different from HC. Therefore, we suggest that a greater degree of abnormal deactivation of the left DLPFC may be associated with a poorer response to SNM therapy, which would need to be confirmed by further expansion of the sample size of the failure group.

One limitation of this study is that fNIRS can only reach the cerebral cortex with limited detection depth, resulting in changes in the activation of the deep brain nucleus that cannot be measured. Another limitation is the small sample size of the failure group, which we will expand in the future.

## CONCLUSIONS

We found abnormal deactivation of the left DLPFC (BA 9) in OAB patients, which may release inhibition of the DLPFC on the voiding reflex, leading to socially inappropriate involuntary urination, which may be the central pathogenesis of OAB. A possible central mechanism of SNM for OAB is to restore activation of the left DLPFC and the inhibition on voiding reflex to near normal levels. Compared with the success group, the failure group showed abnormal deactivation of left DLPFC (BA 9), suggesting that a greater degree of deactivation of the left DLPFC may be associated with a poorer response to SNM. Our results may provide important value in understanding the central pathogenesis of OAB and the central mechanism of action of SNM and even may predict treatment response in the future.

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## EDITORIAL COMMENT

Pang and colleagues studied 18 idiopathic overactive bladder (OAB) patients with urodynamically determined detrusor overactivity/OAB symptoms and 16 healthy controls who underwent real-time near infrared spectroscopy (NIRS) pre- and post-peripheral sacral neuromodulation (SNM). They found that OAB symptom score and urodynamic parameters improved after SNM. Brodmann's area 9 was deactivated in the pre-OAB group, and in that group, left dorsolateral prefrontal cortex (PFC) was significantly reactivated after SNM. This is new work.

Previously, based on neurovascular coupling theory, dynamic brain changes relevant to bladder changes have been investigated by single photon emission computed tomography (cerebral blood flow, in normal pressure hydrocephalus before/after brain shunt surgery),[1] functional magnetic resonance imaging (blood oxygen level dependent, in Parkinson's disease before/after deep brain stimulation in the subthalamic nucleus etc,[2] in idiopathic OAB and Fowler's syndrome before/after peripheral SNM) and NIRS (in idiopathic OAB before/after systemic anticholinergics [not easily penetrating the blood-brain barrier]). Findings of these studies, including the current study, are summarized as before intervention, PFC is deactivated and after intervention, PFC is reactivated to the quasi-normal pattern. In Parkinson's disease, this might be brought about by resuming the PFC-basal ganglia D1 dopaminergic pathway that is inhibitory on the micturition reflex.[2]

NIRS needs methodological expertise to obtain good recordings while it allows us to see brain activity in a real-time manner. Therefore, further studies are warranted to see real-time brain activity in more detail relevant to various bladder behavior in future.

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