Functional MRI in patients with detrusor sphincter dyssynergia: Is the neural circuit affected?

Sandra Seseke | Conrad Leitsmann | Sameh Hijazi | Lutz Trojan | Peter Dechent

1Department of Urology, Martha-Maria Hospital, Halle, Germany
2Department of Urology, Georg-August-University, Göttingen, Germany
3Department of Urology, Ibbenbüren Hospital, Ibbenbüren, Germany
4Department of Cognitive Neurology, MR-Research in Neurology and Psychiatry, Georg-August-University, Göttingen, Germany

Correspondence
Peter Dechent, Department of Cognitive Neurology, MR-Research in Neurology and Psychiatry, Georg-August-University, Göttingen, Germany.
Email: Peter.Dechent@medizin.uni-gottingen.de

Abstract
Aims: In recent years, the human brain-bladder control network has been visualized in different functional magnetic resonance imaging (fMRI) studies. The role of the brainstem and suprapontine regions has been elucidated. Especially the pontine region and the periaqueductal gray, as the central structures of the micturition circuit, were demonstrated. Detrusor sphincter dyssynergia (DSD) is a common problem in patients with neurological diseases. Residual urine and consecutive urinary tract infections with the risk of kidney damage remain a problem. In the present study, we used fMRI of the brain to compare the activation sites of patients with DSD with those of our previously published healthy controls with special emphasis on the brainstem region.

Methods: fMRI was performed in 11 patients with DSD who had an urge to void due to a filled bladder. In a nonvoiding model, they were instructed to contract or to relax the pelvic floor muscles repetitively.

Results: In patients with DSD, we could reproduce the activation sites found in healthy subjects, showing the regions in the brainstem as well as the other micturition-related areas. The activation of the pontine region was more rostral/dorsal compared with the healthy volunteers.

Conclusion: Interestingly, we detected the well-known activation in the pontine region in the patients in the dorsal/rostral part compared with the more ventral activation in the healthy volunteers, suggesting that the L-region of the pontine micturition center is more prominent in cases of DSD.

KEYWORDS
detrusor sphincter dyssynergia, fMRI, neurogenic bladder

1 INTRODUCTION

After identifying the brain regions which are involved in the normal micturition control by using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) in the last decades, the next step was to transfer the paradigm to patients with lower urinary tract dysfunction. Several studies identified altered activation levels in those brain structures which are involved in the micturition circuit. Furthermore, a meta-analysis summarized those results using activation...
likelihood estimation. It revealed multiple brain regions including thalamus (bilaterally), right insula, cerebellum, and brainstem (bilaterally) activated during bladder filling and micturition.

Neurogenic bladder dysfunction is a heterogeneous problem in urological practice. Storage and/or voiding symptoms are common in the everyday life of those patients. Still, we cannot predict the success of oral medication, pelvic floor physical therapy, behavioral modification, and even more those of invasive procedures like sacral neuromodulation.

Urgency, frequency, and neurogenic detrusor overactivity are the most common urological symptoms in patients with neurogenic disorders like multiple sclerosis (MS), Parkinson's disease, spinal cord injuries, or ischemic stroke. Dysfunctional voiding occurs in 34% to 79% of the patients. A special subgroup in the neurogenic disorders are patients with detrusor sphincter dyssynergia (DSD). Residual urine and consecutive urinary tract infections with the risk of kidney damage remain a problem in those patients.

In our present fMRI study, we included only patients with DSD in order to minimize the heterogeneity of the patients' group and to have a more uniform population. Using a nonvoiding paradigm well-established in our lab, the activation sites and levels of these patients were compared with those of healthy controls, previously published by Seseke et al with special emphasis on the brainstem region.

2 | MATERIALS AND METHODS

2.1 | Subjects

Eleven patients (eight females, three males, mean age ± SD: 54.5 ± 14.3 years, age range: 35-77 years) with MS and clinically proven DSD participated in the study. The work-up included urinanalysis, ultrasound, and urodynamics (UD). The UD was performed before the fMRI. As in our previous studies, UD was not performed during fMRI to avoid an even more inconvenient situation for the patients. Furthermore, we also wanted to apply exactly the same experimental paradigm as previously applied. Only patients with monosymptomatic DSD and without any signs of urinary tract infection, detrusor overactivity or prostate-related bladder outlet obstruction were included. The pelvic floor exercise was explained before the fMRI examination to familiarize every participant with the task. The formerly published healthy control group consisted of 22 healthy volunteers (11 females, 11 males: mean age ± SD: 31.2 ± 10.5, age range: 19-49 years) without any history of neurological or psychiatric disease. While hardware and software of the MR scanner were different for healthy controls and patients, the experimental task performed by the two groups was exactly the same. The local ethical committee approved the protocol and all subjects were included after written informed consent.

2.2 | Magnetic resonance imaging

MR imaging was performed at 3 tesla (Magnetom TIM Trio; Siemens Healthcare, Erlangen, Germany) using the standard 32-channel phased-array head coil. Subjects wearing headphones for noise protection were placed supine inside the magnet bore. Vital functions were monitored throughout the experiment. Initially, an anatomical T1-weighted MR data set covering the whole head at 1 mm³ isotropic resolution was acquired (3D Turbo FLASH; repetition time [TR]: 2250 ms, inversion time: 900 ms, echo time [TE]: 3.26 ms, flip angle: 7°). Functional imaging was performed using a T2*-weighted-multiband gradient-echo echo-planar imaging sequence provided by the Center for Magnetic Resonance Research of the University of Minnesota, with an in-plane resolution of 3 × 3 mm² (TR: 1000 ms, TE: 30 ms, flip angle: 60°, acquisition matrix: 64 × 64, multiband factor: 3). Forty-two sections of 3 mm thickness (distance factor: 10%) angulated in an axial-to-coronal orientation, covering the whole brain and brainstem structures, including the pons, were acquired.

2.3 | Paradigm

The subjects were instructed not to void and to drink properly at least 3 hours before the examination. They sensed a strong desire to void due to a filled bladder at the time of the examination. During the functional experiments, the subjects had either to release pelvic floor muscles to mimic voiding (RELAX) or contract pelvic floor muscles to mimic the interruption of voiding (CONTRACT). Commands were presented visually using a video projector (IN5108; InFocus, Tigard, OR) displaying the commands on a back-projection screen placed in the back end of the magnet bore. Subjects viewed the screen via a mirror on top of the head coil. In an event-related manner, the instructions RELAX and CONTRACT were alternated (2 seconds each), each followed by a control condition (18 seconds) during which the subjects had to lie relaxed waiting for the next instruction. Consequently, a single cycle of RELAX and CONTRACT with respective control conditions lasted 40 seconds. Following an initial control period (20 seconds), each instruction was given 15 times resulting in a total time of 620 seconds for the fMRI experiment. After the investigation, the participants were asked about proper task execution, which was confirmed by every single subject.
2.4 Analysis

Functional data were analyzed and visualized using Brain Voyager QX (Brain Innovation, Maastricht, the Netherlands). Preprocessing included 3D motion correction, slice scan time correction, linear trend removal, and spatial smoothing with a Gaussian kernel (full width at half maximum: 5 × 5 × 5 mm³). Subsequently, functional datasets were coregistered to the anatomical data set and transformed into Talairach space. Group analysis was performed using the multisubject approach of the general linear model. In the first step, the main effects of conditions RELAX and CONTRACT were calculated and the analysis of both conditions using the random effects model was done for all patients. In the second step, the results were compared qualitatively with a formerly studied group of Seseke et al using the data of healthy female and male volunteers. All the MR data were normalized to Talairach space using identical processing steps to allow for an appropriate comparison of activated regions in the patients of this study and control subjects acquired in our previous studies.

The obtained P values of the patient group were corrected for multiple comparisons using the cluster-size thresholding approach.16 Maps were thresholded at an initial cluster-forming threshold with P < .005. The size of the resulting clusters was assessed for significance using Monte Carlo simulations. Reported clusters are significant at a level of P < .05. The healthy subject’s activation maps were corrected for multiple comparisons using a Bonferroni corrected P < .05.

3 RESULTS

All patients underwent UD before the fMRI session. Isolated DSD could be detected in all 11 cases. DSD was defined as a rise of muscle activity in the pelvic floor electromyography during relaxation of the pelvic floor (RELAX), showing that the urethral sphincter muscle contracts, instead of relaxing completely during initiation of voiding. The individual patients presented residual urine between 170 and 425 mL. There were no signs of involuntary detrusor contractions during the filling phase at any time before the instruction to void being given. Two of the patients had slightly decreased detrusor pressure during micturition (p_max 14 cm and 15 cm H2O, respectively).

None of the subjects was able to initiate the micturition, presumably due to subconscious restraint resulting from the inconvenient situation. The activation sites known from the healthy controls6,7 were demonstrated. Again, well-localized activations in the pontine micturition center (PMC) and the periaqueductal gray (PAG) were identified and activations of the main cortical and subcortical structures could be reproduced in the patients. The activation level was weaker than in the healthy volunteers, as already shown in the patients after radical prostatectomy.8 Table 1 lists the peak activations from our group of patients. Figure 1A shows the activation patterns of the main effects of patients and healthy controls, Figure 1B provides a detailed view of the activation patterns of patients and controls in the brainstem. Figure 2 demonstrates the activation patterns of patients and healthy subjects projected onto inflated brain hemispheres.

When comparing the activated regions of the patients with those of healthy volunteers, we found that the pontine activation site was located more dorsal in the patients compared with the healthy controls (Figure 1B, Table 2). Another difference was that the putamen did not show a significant activation. Instead, the globus pallidus was activated (Table 1).

4 DISCUSSION

The micturition-related brain regions in humans could be demonstrated in the last decades using noninvasive neuroimaging. The summary of Fowler and Griffith17 encouraged the investigators to transfer their paradigms to pathological voiding conditions. Since then, only few studies dealt with functional imaging in patients with neurological voiding disorders. Khavari et al9 studied patients with MS. They could demonstrate that the patients show lower, more diffuse activation than the healthy volunteers and recommended to study a larger population of those patients to identify areas of interest for future interventions. Clarkson et al18 analyzed the interaction between activated regions in urge incontinent women before and after therapeutic interventions and concluded that responders and nonresponders to therapy may represent different subsets of urge urinary incontinence. In another study, Tadic et al11 showed that the activity of brain regions involved in the control of continence is related to clinical measures of incontinence severity and could be used to evaluate therapy.

Even fewer studies used fMRI to monitor the brain activity before and after therapeutic intervention to elucidate the effectiveness of treatment. Weissbart et al19 analyzed the fMRI data of women with overactive bladder before and after sacral neuromodulation. They concluded that neuromodulation may be more effective in patients with a higher level of pretreatment brain activity.
The reasons for the restraint are heterogeneous. In patients with neurogenic disorders, the symptoms can affect either the storage or the voiding period. The problem in the evaluation is the heterogeneity of symptoms and lesion localization. We often find a mixture of various symptoms. On the one hand, the overactive bladder is a real burden and affects the everyday life, on the other hand the development of residual urine and the inability to completely empty the bladder can cause impairment of the urinary tract function if unnoticed. Our study focused on the subgroup of patients with DSD in that heterogeneous pool. We tried to keep the group as uniform as possible. The aim was to evaluate the cerebral areas involved in those patients and to elucidate potential differences compared to the healthy volunteers published earlier.6,7 Furthermore, we wanted to challenge the conclusion of Arya et al12 who stated in their meta-analysis that the brainstem areas have not been adequately visualized in existing neuroimaging studies.

Griffith et al5 described the two micturition circuits, which are involved in the healthy. The first covers the resting and the attention needed state and includes the medial prefrontal cortex, the parahippocampal areas, and the PAG. During bladder filling the second circuit is responsible for the perception of urgency and the desire to void and involves the insula and the cingulate cortex. The pontine region remained relatively difficult to assess.12 In our group of patients with DSD we could show, that the areas of those two circuits could be demonstrated (Figures 1 and 2). The comparison of t-values of our patients with those of healthy volunteers published by Seseke et al6,7 revealed lower values in nearly all regions, as shown previously in patients after prostatectomy8 and in patients with MS.9 The PAG as the central structure in regulating the micturition process projects directly to the PMC. The switch between inhibition and permission of voiding via efferent signaling to the pontine region is relayed in that area. Furthermore, the PAG is controlled by the prefrontal

| TABLE 1 | Brain regions activated during both, relaxation (RELAX) and contraction (CONTRACT) of pelvic floor muscles in patients with DSD (n = 11) |
| Region | Hemisphere | x  | y  | z  | Peak activation, t value | Activation size, mm³ |
| Pontine micturition center | –1 | –25 | –36 | 5.1 | 319 |
| Periaqueductal gray | R 7 | –23 | –8 | 7.1 | 539 |
| Cerebellum | L –7 | –21 | –8 | 7.3 | 495 |
| | L 30 | –51 | –28 | 7.3 | 3800 |
| Vermis | – | – | – | – | – |
| Thalamus | R 9 | –13 | 3 | 8.1 | 2297 |
| | L –8 | –15 | 3 | 10.5 | 2889 |
| Globus Pallidus | R 20 | –6 | 0 | 6.5 | 781 |
| | L –25 | –8 | 0 | 6.7 | 880 |
| Insula | R 48 | 9 | 7 | 8.7 | 1008 |
| | L –36 | 9 | 7 | 8.1 | 964 |
| Inferior frontal gyrus | R 49 | 5 | 13 | 6.2 | 2316 |
| | L –49 | 4 | 9 | 6.9 | 402 |
| Occipital cortex | 0 | –83 | –11 | 4.9 | 416 |
| Inferior parietal lobule | R 55 | –35 | 26 | 7.7 | 4000 |
| | L –52 | –30 | 23 | 6.2 | 6623 |
| Pre-SMA | –1 | 7 | 49 | 9.1 | |
| SMA | –2 | –13 | 52 | 7.2 | |
| Sensorimotor cortex | R 19 | –30 | 56 | 6.2 | |
| | L –14 | –28 | 61 | 5.9 | 32980a |

Note: All areas known from the healthy volunteers (Seseke et al6,7) are listed. Additional areas specifically activated in our patient group are shown in italics.
Abbreviations: DSD, detrusor sphincter dysynergia; L, left; R, right; SMA, supplementary motor area.

*Summed activation size of contiguous brain regions.
FIGURE 1  A, Activation patterns revealed by the analysis of the main effects of patients with DSD (n = 11, orange) and a group of the healthy controls (n = 22, blue) overlaid on an anatomical data set of a single patient. B, Magnified views of the brainstem. Well-localized activations are identified in the pontine micturition center. The patient's activations were detected more dorsal/rostral. DSD, detrusor sphincter dyssynergia; PMC, pontine micturition center.

FIGURE 2  Activation patterns revealed by the analysis of the main effects in patients with DSD (top, n = 11), healthy controls (bottom, n = 22), and the overlay of both groups (middle); same data as in Figure 1. Results are superimposed on the inflated hemispheres of an individual brain. The left and the right hemisphere are shown in lateral as well as medial views. A = PAG, B = inferior frontal cortex, C = inferior parietal cortex, D = insula, E = pre-SMA, F = SMA, G = sensory-motor cortex. DSD, detrusor sphincter dyssynergia; PAG, periaqueductal gray; SMA, supplementary motor area.
cortex and hypothalamus, as well as insula and anterior cingulate cortex. These activations can be visualized in our group of patients. The whole circuit is summarized in the review of Fowler et al.17

In addition, we could reveal some differences between DSD patients and healthy controls. Surprisingly, the pontine region showed a completely different activation site in the group activation map of the patients. The activation was detected in the more rostral/dorsal part in the DSD group (Figure 1B). Furthermore, some of the patients showed additional activation in the ventral part (Figure 1B). Is it explained by a stronger activation of the pontine L-region as the patients have to try harder to initiate the micturition and the urethral sphincter is inhibited as functional brain studies of Blok et al2 and Nour et al20 elucidated? The region described in those studies is located a bit more laterally with a right-sided predominance we could not find in our data. The activations could be demonstrated in our patients as well as in the study of Blok et al,2 but only in those subjects who were unable to void. In the cat, the same pontine region corresponds with the L-Region which is responsible for continence control.21 The more ventrally located activation in our group of healthy volunteers6,7 may rather be the M-region as the inhibition of the urethral sphincter is not compromised in the healthy. Perhaps we identified the functionally distinct pontine regions in patients and healthy controls. In a recent study of Keller et al22 using an animal model, neurons in the PMC expressing estrogen receptor 1 were identified, which are responsible for bladder contraction and relaxation of the urethral sphincter, whereas the other subset of neurons found, expressing corticotropin-releasing hormone, only increased the bladder pressure. The study could show that molecularly and functionally distinct cell groups may play a role in the subcortical regulation of micturition. In human, further studies with larger samples have to clarify the location differences in functional mapping of the pontine regions.

In contrast to healthy volunteers, formerly published by Seseke et al6,7 the well-localized activation of the putamen could not be reproduced. Instead, the globus pallidus was activated bilaterally. In cats, Lewin and Porter23 observed inhibition of bladder activity and in consequence of the micturition reflex by stimulating this region. Activation of the globus pallidus has been detected during bladder filling.20 The activation in our DSD group might be a result of the inability to initiate voiding.

The special role of the basal ganglia was underlined by Khavari et al.9 In their small subgroup of three patients with DSD they could show that the caudate nucleus as a processing center of motor function was activated stronger compared with patients with MS but without

### TABLE 2 Localization of pontine activation in the individual patients with DSD (n = 11)

| Pat no. | Talairach coordinates, mm | Peak activation, t value |
|---------|--------------------------|--------------------------|
| Dorsal part | | |
| 1 | 4 | −26 | −26 | 6.5 |
| 4 | 0 | −22 | −37 | 6.4 |
| 5 | −2 | −33 | −35 | 4.9 |
| 7a | 0 | −30 | −28 | 6.5** |
| 8 | 0 | −26 | −33 | 8.8 |
| 9a | 5 | −28 | −27 | 7.0 |
| 10 | 0 | −33 | −35 | 2.6a |
| 11 | 0 | −35 | −33 | 3.5** |
| Ventral part | | |
| 2 | 0 | −22 | −32 | 11.0 |
| 3 | 0 | −21 | −33 | 4.6 |
| 6 | 0 | −20 | −32 | 8.0 |
| 7a | 2 | −19 | −29 | 6.9** |
| 9a | 6 | −19 | −29 | 7.3 |

Note: All P < .005 corrected for multiple comparisons (P < .05), except *P < .05 uncorrected and **P < .005 uncorrected.

Abbreviation: DSD, detrusor sphincter dysynergia.

aTwo patients showed a ventral as well as a dorsal activation site.

*P < .05.

**P < .005.
DSD. They concluded, that this could be explained by the fact that those patients with DSD perhaps need more abdominal straining and compensatory mechanisms to initiate voiding against a higher bladder outlet resistance. However, in our group of patients, we could not show the area activated.

Certainly, we have to discuss some study limitations. Although we tried to keep the group as uniform as possible, we may have some selection bias, as we only included patients compliant with the fMRI examination. Furthermore, we did not take into account the lesion load and lesion localization of the individual patients. Theoretically, the individual activation patterns could be influenced by the site of the lesions and general white matter pathology. However, it is suggested that both, number of lesions and white matter variations, do not play a crucial role regarding the disability of the patients. The nonvoiding model we used has pros and cons. On one hand, as the patients only mimic voiding, it is not really a “micturition related” paradigm, but on the other hand, we can avoid catheter artifacts to make the situation even more inconvenient for the patients. We did not use a quantitative comparison to the healthy control group, as it was part of a former study and the interval between the group analyses was too long, including a change of the hardware and the software of the scanner. Nevertheless, the qualitative analysis revealed robust matches in the areas involved in the micturition cycle. In any case, our nonvoiding paradigm allows for the identification of common micturition-related brain regions as summarized in. The strength of our study is the homogeneity of the patient group. We elucidated one single criterion of the heterogeneous symptoms of patients with neurogenic bladder. In summary, fMRI in patients with neurogenic bladder allows to visualize region-specific brain activation changes and contributes to a better understanding of the dysfunction. It may be useful for pretreatment evaluation and for assessment of therapeutic response. Until then we still need studies with larger samples of patients, whose symptoms are as uniform as possible, to further characterize neural aspects of the disease.

5 | CONCLUSION

In the present study we used fMRI to investigate the micturition-related brain circuits in patients with DSD as a subgroup of neurogenic bladder disorders. We tried to characterize similarities and differences in the brain activation patterns of patients with DSD. Compared to healthy subjects, the regulation areas could be detected and differences could be found especially in the brainstem and a part of the basal ganglia. The main effects were comparable with those of a group of healthy subjects. Interestingly, we detected the well-known activation in the pontine region of the patients in the dorsal/rostral part, suggesting that it is a stronger activated L-region as the patients are unable to relax the urethral sphincter properly in contrast to the healthy volunteers in which we found the activation more ventrally. Further studies will be needed to prepare the use of the method for pretreatment analysis and follow-up of therapeutic interventions.

ORCID

Sandra Seseke http://orcid.org/0000-0002-7700-9623

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