

INUS Neuro-Urology News

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Interview with the Expert

Abnormal Resting-State Network Presence in Females with Overactive Bladder

Dr. Ulrich Mehnert, MD, PhD (CH)

Senior Consultant, Department of Neuro-Urology
Balgrist University Hospital, University of Zurich

Dr. Glenn Werneburg, MD, PhD (US)  @gwerneburg
INUS Early Career Officer; Editor, NUN



In this issue of Neuro-Urology News, I had the opportunity to interview Dr. Ulrich Mehnert at his home institution of Balgrist University Hospital, in Zurich, Switzerland.

Dr. Mehnert earned his Medical Degree in 2004 from Ulm University, Germany. He started his urology residency in the Department of Urology and Pediatric Urology at the University Medical Center Schleswig-Holstein, Kiel, Germany, under supervision of Prof. K.-P. Jünemann. From 2006 to 2009, Dr. Mehnert worked as a resident and postdoctoral research fellow in the Neuro-Urology unit of the Spinal Cord Injury Center at Balgrist University Hospital under supervision of Prof. B. Schurch. In 2010, he continued his training in urology with focus on surgical therapy in neuro-urological patients at the Hôpital Pitié-Salpêtrière, Sorbonne University, Paris, France under supervision of Prof. E. Chartier-Kastler and Prof. M. O. Bitker.

From 2011 to 2014, Dr. Mehnert completed his specialty training in urology under supervision of Prof. J. Noldus in Urology and Neuro-Urology at the Marienhospital Herne, Ruhr University Bochum. Subsequently, he returned to Balgrist University Hospital where he worked as consultant and then senior consultant urologist in the Department of Neuro-Urology. In 2018 he earned his sub-specialization certificate in Neuro-Urology and PhD from the University of Maastricht, The Netherlands. Dr. Mehnert is Vice-Chairman of the Swiss Continence Foundation, and co-founder and the first Treasurer of the International Neuro-Urology Society (INUS).

Dr. Mehnert is the author of more than 60 peer-reviewed publications and is the principal investigator

for several research grants (including from the Swiss National Science Foundation). His main research interests comprise the investigation of supraspinal lower urinary tract control and the neurophysiological assessment of lower urinary tract dysfunction. In this interview we discuss his group's recent work and publication "Abnormal Resting-State Network Presence in Females with Overactive Bladder", published in Biomedicine in June 2023. Below is our interview, edited for length and clarity.

Dr. Glenn Werneburg: What is known about the etiology of overactive bladder?

Dr. Ulrich Mehnert: It has been suggested that there are different etiologies of overactive bladder (OAB), but the difficulty is to phenotype patients to understand their different etiologies. There is clinical heterogeneity in the condition, and we still have not found the adequate biomarkers. For example, some individuals have detrusor overactivity, and some do not. Some will adequately react to treatment with anti-muscarinic agents, others will not. There are hypotheses that the OAB etiology is related to the bladder itself (detrusor and/or mucosa dysfunction), the peripheral nerves including nerve terminals within the bladder or to the brain, and/or behavioral issues. With regard behavior, you could, for example, imagine someone who mainly works at a desk and gets into the habit of regularly going to the toilet and emptying the bladder even when there is no desire to urinate, simply to have a reason to get away from the screen. If practiced over a longer period of time, this could lead to a change in the set point of bladder perception in the brain and, with further change in the set point, may lead to disturbing OAB symptoms.

INUS Calendar

INUS Course
3rd Course of Reconstructive Surgery for Spinal Cord Injury Patients
Santiago, Chile
March 22-April 23, 2024

INUS Course at EAUN Meeting
Paris, France
April 6-8, 2024

INUS Session at Annual Congress, Urologic Society of India
Hyderabad, India
April 19-20, 2024

INUS International Course on Neuro-Urology
Bangkok, Thailand
June 27-28, 2024

INUS International Course on Neuro-Urology
Medellin, Columbia
September 27-28, 2024

INUS Annual Congress 2025
Zermatt, Switzerland
January 16-18, 2025

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GW: What was the impetus for this current study?

UM: Most of the available therapies for overactive bladder target the bladder, but I think the bladder should not be the sole focus. In fact, maybe the bladder is the innocent bystander, and the main problem is the brain, which is an important and complicated structure. Thus, the impetus for the study was to assess networks in the brain that may differ between those with and without overactive bladder. The data here ultimately could lead to insights regarding the pathophysiology of OAB and/or novel therapeutic targets.

Motor function is much simpler than bladder function, in my opinion. You activate your motor cortex and, via two motor neurons, the leg moves. That's the whole story. To the contrary, in lower urinary tract control, there is not a single area but a whole network involved including emotional centers controlling spinal switching nodes on multiple layers. In relation to bladder control, a series of different questions become relevant: How do I feel? Is it safe and socially acceptable to empty the bladder now? Am I observed? How is my emotional situation?

There could be an element of embarrassment and thus the decision to defer voiding. In addition, there are brainstem centers involved because, in our biological history, urination had a very close relationship to survival. Historically, these might include marking an area or smelling the fertility of the other gender. While humans don't use urine in this way anymore, I believe such associations still remain within nuclei in our brainstems that are involved in lower urinary tract control. Maybe this explains why there is often a sense of embarrassment around lower urinary tract dysfunction. Loss of urine, or loss of the ability to void could be associated with loss of control and thereby, in a broader sense, loss of participation in the species' fundamental survival strategies. In this regard, it is

very interesting to see how people have no problem reporting in public about other health problems such as a heart attack. This is the case even if they themselves caused it through a completely unhealthy lifestyle, while problems with the urinary bladder, especially incontinence, are completely taboo. Thus, as urologists, we need to treat the bladder, but also consider the whole story – including the relevant psychological aspects.

GW: Explain resting-state functional magnetic resonance imaging and its potential applications to voiding dysfunction.

UM: Resting state functional MRI is as the name suggests: imaging in the resting state condition. It assesses the brain when it is not performing any specific task. In general, our brain always has some basic activity, which is necessary to be able to prepare for potential things that come up. It's like a tennis player waiting for the serve. There are different resting state brain networks that may switch based on what an individual expects to come or what happened last time. In this study we investigated the presence of the resting state networks and the ability to switch among them in healthy subjects versus those with OAB and to correlate the observed deficiencies with the clinical symptoms. This should help us to better understand to what extent patients with OAB differ from healthy people in their supra-spinal coordination even in "rest mode" and to what extent this influences their OAB problem.

GW: Describe the design of the current study. What was your hypothesis?

UM: Regarding the study design, we performed a resting-state MRI scan of the brain in a selected group of healthy individuals and those with OAB. This examination takes a few minutes. The participants lay in the scanner with an empty bladder. An independent component analysis was then carried out with the data to identify the large-scale networks as well as a region of interest (ROI)-to-

ROI and seed-to-voxel analysis in order to show detailed connectivity between specific brain areas. The results of the seed-to-voxel analysis were then correlated with the clinical symptoms from the 3-day bladder diary. We hypothesized that at least part of the OAB problem or bladder control problem is related to brain function, and that specific areas of the brain are involved and not communicating well in this condition. These changes or deficits in communication between areas can be very subtle, which is why on the one hand they cannot be discovered as part of a routine clinical examination, but on the other hand they can be sufficient to cause disruptions, especially in complex network systems such as urinary bladder control.

GW: How did you define the clinical outcomes in this study? What were the main differences between individuals with OAB and controls?

UM: The study outcome was, on the one hand, information about the presence and strength of the resting-state networks as well as the supraspinal connectivity between individual centers in both the group of healthy people and in the group of individuals with OAB and the difference between the two groups. Here it was shown that the healthy people had a significantly stronger presence in the resting state networks as well as a stronger connectivity between individual areas that are known to be involved in the control of the lower urinary tract. In contrast, the OAB group had deficits in comparison to the healthy controls. Now we didn't just want to show the pure differences between the two groups, but also assess the extent to which different findings in the OAB group had influence on their OAB symptoms, such as number of urgency episodes. Here it was shown that the weaker the bladder contractility in the OAB patients, the more frequently emergency episodes occurred.

GW: What are the clinical implications and what are the next steps of the present study? Do you plan to determine what's the cause and what's the effect?

UM: This study is of course more likely to be classified as a basic study, even though patients were examined, so there is no immediately implementable clinical implication. Nevertheless, the study can significantly contribute to our understanding of OAB and how the approach to this problem in individual patients could be adapted in everyday clinical practice in the future. We hope that in the future it will be possible to phenotype our OAB patients with such examinations and that we will not only focus therapeutically on the urinary bladder but also include more supraspinal therapy options. Such therapeutic options could already include behavioral therapy and autogenic training, especially if one takes into account that the urinary bladder is primarily controlled by the autonomic nervous system.

There are different forms of autogenic training, one of which is biofeedback. In general, autogenic training is a technique for relaxation wherein there is promotion of calm and relaxation in the body with the goal of reducing anxiety, stress, or other adverse conditions. In some ways, it is a form of meditation. Some urgency incontinence has been described as “keyhole urgency”, wherein it starts at precisely the time an individual enter his or her house (puts the key in the hole in the door). Clearly, this is somehow related to a cognitive nerve issue as the brain already knows the toilet is nearby. So an interesting question is whether this can be actively suppressed. I'd hypothesize it would be easier to do this in individuals without proven detrusor overactivity than those with proven detrusor overactivity.

To determine exactly the cause and effect, we would need to perform longitudinal studies. We would select patients and follow them over time to assess how symptoms and brain changes develop. But that is a larger project to plan.

GW: Do you suspect the principles and the findings in your study might apply to other urologic conditions like pain syndromes?

UM: Absolutely. A major issue regarding our management of bladder pain syndromes is that we often do not completely know the pathway and life experiences of our patients that have led to our encounter. Because, unfortunately, some people with bladder pain syndromes are at first not taken seriously, this can aggravate the situation because they are desperate for help, as they may not have yet received it leading up to their current presentation. As neuro-urologists, we need to consider this. We need to address the pain, but also the other relevant factors of the patient and his or her experience. I'm not sure we can solve or improve this with brain imaging, but it can give us an idea of what is happening in the context of pain. One example is phantom limb pain syndrome following a limb amputation. Pain in this context can be improved through biofeedback using MRI. Individuals can see their brain activity in real time and can try to modulate it. So this could be very interesting, and perhaps effective, for OAB and pain. The entities certainly have some common aspects. Maybe in a subset of patients, if OAB is left untreated, it could progress to pain.

GW: What advice do you have for junior INUS members embarking on careers as physician scientists with a neuro-urology focus?

UM: Neuro-urology is a very interdisciplinary subject that would really benefit from clinicians who are also involved in scientific research, and also from basic scientists learning clinical medicine. Those who both see patients and do research are able to deeply understand the problems of the patients and to develop a good research question to test in the lab.

To that end, we also need good collaboration between physicians and scientists. The research in neuro-urology and neurobiology is quite complex and you usually require a team because the tech-

niques are quite sophisticated. In my case, I need other people to help me do the measurement, perform the interpretation of technical assays, and so on. I would encourage physicians to not only invest their time in clinical care, but also be involved in research. It can be a gratifying career to do both. For example, I not only want to be a doctor to talk to the patient and offer them the available treatments, but I want to have influence through research on what treatments are offered. I think I can be a better consultant for the patient because I have invested time in research and have developed a deeper understanding of the pathophysiology of functional urologic conditions.

Additional Reading:

de Rijk, M. M., Drake, M. J., von Gontard, A., Solomon, E., Dmochowski, R., Schurch, B., & van Koeveringe, G. A. (2023). Functional neuroimaging related to lower urinary tract sensations: Future directions for study designs and selection of patient groups: ICI-RS 2023. *Neurourology and Urodynamics*.

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Mehnert, U., Walter, M., Leitner, L., Kessler, T. M., Freund, P., Liechti, M. D., & Michels, L. (2023). Abnormal Resting-State Network Presence in Females with Overactive Bladder. *Biomedicine*, 11(6), 1640.

Meet the Board Member

Dr. Kadir Onem (TR)

INUS Research Officer

Fellow of the European Board of Urology,
Associate Professor, Department of Urology, Ondokuz Mayıs
University Medical Faculty, Samsun/Turkey

Dr. Kadir Onem obtained the Medical Doctor Degree from the Medical Faculty of Istanbul in 2002. He started his residency program at the Urology Department at Istanbul University Medical Faculty in 2002 and became urology specialist in 2008. He worked at Kastamonu State Hospital from 2008 to 2011.

In 2011 he became Assistant Professor in the Department of Urology at Ondokuz Mayıs University Medical Faculty, the hospital in which he was born in Samsun. He spent one year as a Postdoctoral Research Fellow of the Neuro-Urology, Reconstructive Urology and Oncology in Baylor College of Medicine at Houston, Texas between 2013-2014. (host: Dr. Christopher Smith, Dr. Seth Lerner). He became Associate Professor in 2017 at Ondokuz Mayıs University.



Dr. Onem with his family.

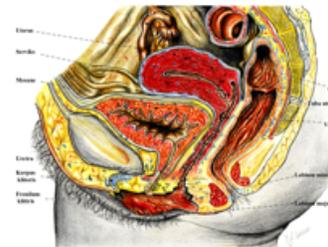
Dr. Onem provides clinical consultation for adult and pediatric patients with neuro-urological disorders, and those who require or have undergone urinary reconstruction. He is also interested in female and male incontinence, urodynamics, pelvic organ prolapse, sacral neuromodulation, urinary reconstruction and additionally bladder cancer. Dr. Onem frequently performs bladder reconstruction. In clinical practice he also is interested in bladder cancer management and neobladder creation, of clinical interest to him since his residency. He is the primary investigator of several international phase III and IV studies regarding neurogenic bladder and bladder cancer (abobotulinumtoxinA in neurogenic patients, adjuvant atezoluzumab for bladder cancer, and others). He was the top recruiter in these studies worldwide. Dr. Onem has several national and international prizes and more than 70 national and international publications and book chapters. He defined surgical techniques in neuro-urology and reconstructive urology fields (Onem Conduit for continent cutaneous diversions, navigation-assisted sacral neuromodulation). He is reviewer for several medical national and international journals. He has a large neurourology database at his faculty hospital. He also has interest and expertise in statistical analysis.

Dr. Onem is a founding member of the Neu-



ro-urology / Incontinence group of Turkish Association of Urology (TAU). For more than eight years, he has been in the TAU Neuro-urology group working on multicentric clinical studies related to neurogenic lower urinary tract dysfunction. Dr. Onem is a member of ICS (International Continence Society) terminology discussion group and associate member at ESFFU (EAU Section of Female and Functional Urology Group) and board member of TAU Blacksea region of Turkey. He was elected as Board Member of International Neuro-urology Society as Research Officer in 2023.

His wife, Gökçe, is an artist and also a management scientist. She also draws medical illustrations for Dr. Onem's studies. He has a 13 year old daughter named Zeren and 15 year old son named Kerem. He enjoys taking nature photographs. He also likes playing computer games with his son, and enjoys traveling. He likes to get out of the city and into nature at every opportunity.



One of
Gökçe's
medical
illustrations

INUS Annual Congress, Zermatt, Switzerland, Winter, 2025

