Bladder Dysfunction in the Context of the Bladder-Brain Connection

Blaasdisfunctie in het kader van de blaas-brein connectie

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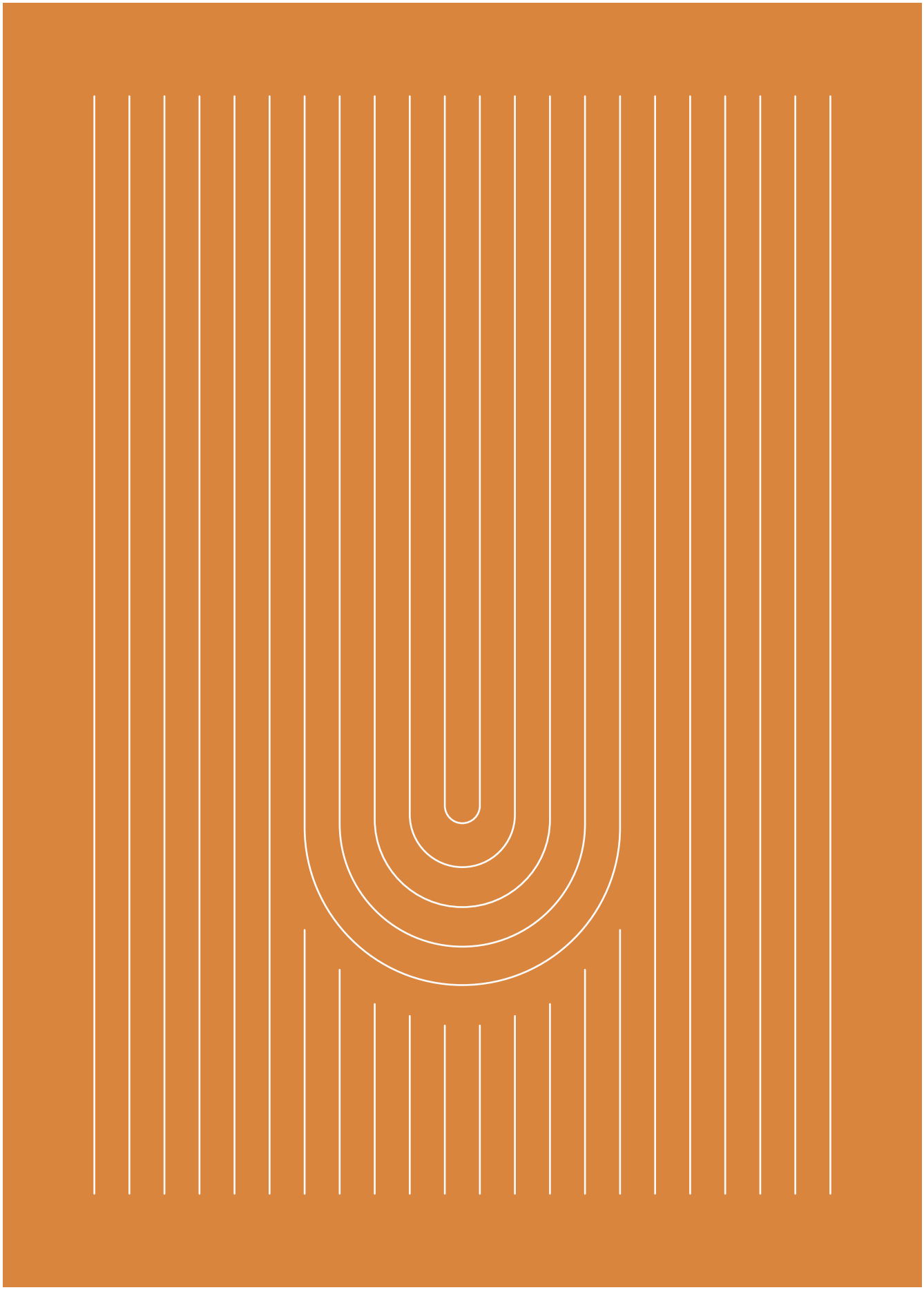
Heelal

Hoe verder men keek
Hoe groter het leek

Jules Deelder

CONTENTS



CHAPTER 1

Introduction

1.1 THE URINARY TRACT

The urinary tract manages the transportation and storage of urine and consist of the upper urinary tract and the lower urinary tract (LUT). The upper urinary tract includes the kidneys and the ureters. The LUT consists of the urinary bladder, the urethra, the external and internal urinary sphincters and the pelvic floor muscles; its anatomy differs between men and women. Although the ability to void at a socially appropriate place and time does not seem like a complex task for human being, it requires the proper functionality of many different complex pathways within the body. Disorders of the LUT (functional bladder disorders) create symptoms of the LUT. This thesis aims to improve our knowledge on diagnostics and treatment of such disorders and symptoms in the context of the bladder-brain connections.

The micturition-cycle is divided into the storage phase and the voiding phase. During the storage phase the detrusor muscle in the bladder wall is relaxed, creating a low-pressure bladder without feeling the urge to void. If the amount of urine exceeds a certain threshold, an urge to void is felt. The voiding phase may start if we are in an appropriate place to void. During the voiding phase the external urethral sphincter relaxes, the detrusor muscle contracts, and the bladder empties. When voiding stops, the storage phase starts again.

1.2 INNERVATION OF THE LUT

The ascending and descending innervation of the LUT is warranted by three nerves (fig 1). Visceral information from the bladder, bladder neck and urethra, is sent to the pons and higher brain areas via both the hypogastric nerve (sympathetic) and the pelvic nerve (parasympathetic). These nerves are furthermore responsible for the descending autonomic innervation of the bladder. The somatosensory control and the motor control of the external urethral sphincter and genitalia are regulated through the pudendal nerve.[1] The areas in the brain and brainstem involved in somatic and autonomic control of the LUT differ as to the specific task of the LUT. The precise working mechanism of these structures in the control of the LUT has not yet been completely clarified. The knowledge in this field is increasing rapidly, however, partly due to the evolution of dynamic brain imaging. Dynamic brain imaging captures the location of activation or deactivation in the brain over time during a specific task. The central innervation of the LUT in healthy subjects has been investigated using dynamic brain imaging but literature is still scarce. Furthermore, these techniques are prone to artefacts, and interpretation of the results is complicated. When focusing on LUT control, some brain areas are specifically studied. The cortex of the brain includes the primary motor cortex and the primary sensory

cortex, each representing a map of the whole body, known as the homunculus.[2, 3] Other brain areas or systems thought to be involved in LUT control are the prefrontal cortex, the basal ganglia, the limbic system, the thalamus, the cerebellum, and the pons.[2, 4]

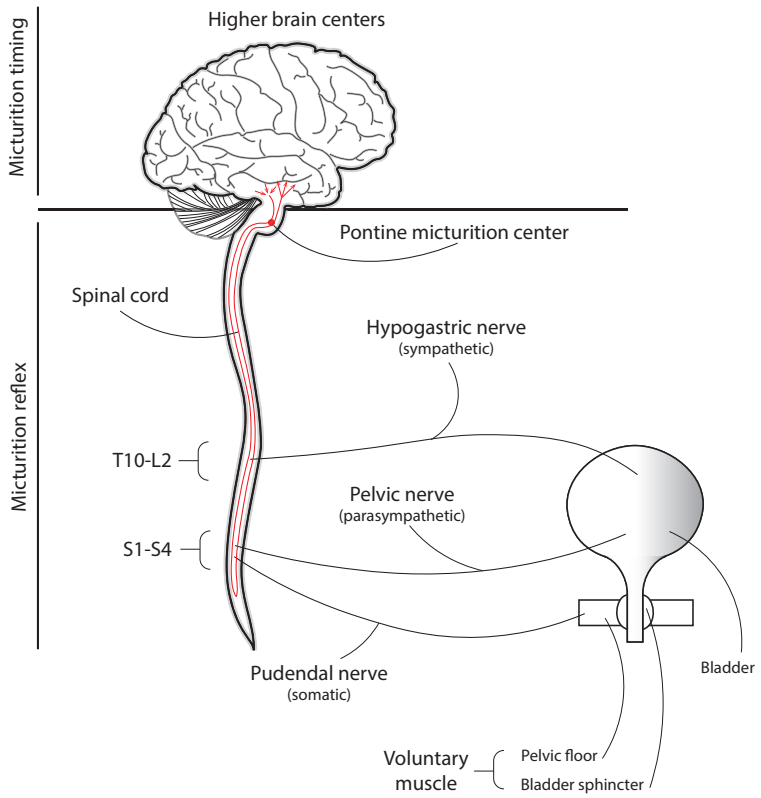


Fig. 1. The innervation of the LUT

1.3 FUNCTIONAL UROLOGY - DISORDERS OF THE LUT

LUT symptoms (LUTS) are divided into *storage symptoms* and *voiding symptoms*. The pathophysiology of LUT disorders is still unknown, but research suggests that it is multifactorial, with the pelvic floor muscles and the central innervation playing an important role.[5, 6] The prevalence of LUTS worldwide ranges from 45% to 64%, which implies that about one in two people will experience at least one LUTS in their lives. Although the mortality of LUT disorders is very low, the negative impact on the quality of life (QoL) appears to be huge. Given the increase of symptoms with increasing age, and the steady increase in life expectancy, LUTS are a major healthcare problem with an

increasing significant economic and social burden.[7-10] The economic burden in the USA was estimated at > $ 9 milliard a year and ranges between countries in Europe from € 333 million to € 1.2 milliard per year.[11, 12] Social embarrassment and shame prevents patients with urinary incontinence (UI) and other LUTS, from seeking help and treatment. Consequently, these symptoms are underexposed and the currently estimated prevalence is most likely underestimated.[13, 14]

Storage symptoms can present in the form of UI, increased daytime frequency, urgency, and nocturia. Urinary incontinence is sub classified into urgency UI , stress UI and mixed UI. Urgency UI is involuntary urine leakage accompanied by or immediately preceded by urgency. Stress UI is involuntary urine leakage on effort or exertion, or on sneezing or coughing. Mixed UI is both urgency UI and stress UI together.[15] *Voiding symptoms* can present in the form of hesitancy, slow stream, intermittency, the feeling of incomplete emptying and post-micturition dribble.[15]

Within functional urology, various syndromes have been described, e.g. overactive bladder (OAB), underactive bladder (UAB) and the bladder pain syndrome (BPS). The latter is included in the LUT domain of chronic pelvic pain.[16] OAB and UAB can present concomitantly.

OAB has the highest prevalence of more than 10% worldwide,[7] and is characterized by *storage symptoms:* urinary urgency, with or without urgency UI, usually with urinary frequency and nocturia, if there is no proven infection or other obvious pathology.[17]

UAB is defined as having *voiding symptoms:* slow urinary stream, hesitancy and straining to void, with or without a feeling of incomplete bladder emptying sometimes with storage symptoms.[18]

The *BPS* is persistent or recurrent chronic pelvic pain, pressure or discomfort perceived to be related to the urinary bladder, accompanied by at least one other urinary symptom such as an urgent need to void or urinary frequency.[19]

As described above, an intact innervation of the LUT is essential for a proper function of the LUT. Within functional urology it is important to distinguish non-neuro-urological patients from neuro-urological patients. In neuro-urological patients, the innervation is disturbed due to a known neurological disorder, for instance spina bifida (congenital) or multiple sclerosis (acquired). Different disorders of the LUT can occur in this patient group, such as low bladder compliance or dysfunction of the pelvic floor muscles which create various symptoms, like UI, the inability to empty the bladder properly or recurrent urinary tract infections. Proper treatment and follow-up are very important to preserve kidney function in neuro-urological patients.[1, 20]

1.4 DIAGNOSTIC TOOLS IN FUNCTIONAL UROLOGY

Two different types of diagnostic measurements are often used within functional urology. *Traditional measurements* assess an objective outcome, such as number of voids per day, voided volume, pad weight or post-void residual. *Patient reported outcome measurements* (PROMS) are subjective outcomes and indicate a patient's perception, usually obtained through a questionnaire.

A simple but important traditional diagnostic tool within functional urology is the bladder diary or voiding frequency chart. It gives information on the frequency of voiding per day and night, and on the average bladder capacity and fluid intake. In the outpatient clinic, a uroflowmetry can be performed after which the post void residual can be measured. The uroflowmetry measures the strength of the stream, which can provide information of the urethra and the tension of the pelvic floor muscles. A more invasive investigation is a urodynamic study, in which, using pressure sensors, the compliance and strength of the detrusor muscle can be measured. Detrusor overactivity and underactivity, which can occur in patients with OAB or UAB respectively, can be detected using a urodynamic study.[18, 19] Because neuro-urology patients might be at risk for high pressure bladders, urodynamic studies in these patients are important investigations in the follow-up.[1]

The field of functional urology often uses *PROMS,* because the differences between objective and subjective outcomes are evident in this field. For instance, an individual might have a negatively affected quality of life (QoL) due to one incontinence episode per day, while the influence of this amount of UI would hardly affect another person's QoL. With the use of PROMS, we can make these perceptions measurable and comparable between patients or within patients over time. Since the evolution of PROMS, many questionnaires have been developed measuring different aspect of different diseases. It is important that PROMS are phrased in line with the patient's language and that questionnaires are validated in this language. Validation of a questionnaire ensures that the questionnaire actually measures what it is supposed to measure. In the Netherlands, some PROMS on diseases in the field of functional urology have been translated and validated in Dutch.[21-29]

As the pathophysiology of diseases in functional urology is still not completely known, tools to confirm or reject suspicion of a certain disease of a LUT disorder are still lacking. Dynamic brain imaging has been postulated as a possible future diagnostic tool in clinical practice. Some important issues need to be addressed, however, before this technique can be implemented in clinical practice. For example, how is the central innervation of the LUT organized and does the central innervation of the LUT differ between patients with LUT disorders and healthy subjects?

1.5 DYNAMIC BRIAN IMAGING

The brain represents about 2% of the adult total body weight but consumes an estimated 20% of the oxygen entering the body. To conserve energy, the brain regulates its blood flow such that active neurons with increased metabolism receive more blood than relatively inactive neurons. Dynamic brain imaging is predicated on this principle and therefore an indirect measurement of neuronal activity. In positron emission tomography (PET) the increased decay of unstable positron-emitting isotopes in areas with an increased metabolism is used to study changes in regional cerebral blood flow.[2, 30, 31] This technique is minimally invasive except for the injection of isotopes in the bloodstream. In functional magnetic resonance imaging (fMRI), the blood oxygenation level-dependent (BOLD) signal is used, which is a signal intrinsic to the brain, without the radioactivity used in PET. Hemoglobin in blood slightly distorts the magnetic resonance properties of hydrogen nuclei in its vicinity. Therefore, the change from oxygenated blood (with hemoglobin), to deoxygenated blood (without hemoglobin) is detectable using fMRI.[2, 31] Its non-invasive character makes repeated observations possible, which constitutes a major advantage over PET.[31] The strength of the magnet in the MRI scanner corresponds with the resolution of the acquired data and is expressed as Tesla. The first 7-Tesla MRI scanners have been installed in the Netherlands, allowing to acquire high resolution images and thus a more accurate understanding of the organization in the human brain.[32]

Most researchers using neuroimaging perform group analyses which reveal a group's average brain response. These results cannot be translated to individuals, however, as we do not know the responses and inter-individual differences in individuals. Clinical application of this technique to detect abnormalities in activity patterns in individuals with specific symptoms is therefore not yet achieved. Defining the involved brain areas and activity patterns of the LUT in healthy individuals is a necessary step towards using this technique in clinical practice.

1.6 THERAPY

Different treatments are available in the field of functional urology, ranging from conservative/non-invasive to pharmacological and invasive therapies. As most of the LUT diseases are non-lethal, the decision to undergo an invasive treatment should always be a shared decision between the patient and urologist in which the risks and benefits have to be considered carefully. Usually a step-wise approach is executed starting with *conservative therapies*.[20, 33, 34]

Conservative therapies include life style interventions (e.g., weight loss, fluid intake or physical exercise) and pelvic floor muscle training. Although effectiveness of these non-

invasive therapies has been proven, patients' therapy adherence decreases on the long term and causes the effect of these therapies to fade.[35, 36] Evidence suggests that pelvic floor muscle training is effective not only in patients with stress UI, but also in patients with urgency UI, mixed UI, pelvic organ prolapse or bowel dysfunction.[36]

Many different *Pharmacological therapies* are available in functional urology. Antimuscarinics have been the cornerstone in pharmacotherapy of OAB. Although various antimuscarinics differ in pharmacological and pharmacokinetic profiles, the use of the majority of these agents is limited because of the suboptimal efficacy or bothersome side effects in particular dry-mouth and constipation.[37, 38] In 2013, the first beta3 agonist became clinically available: mirabegron.[33] As the working mechanism is different from that of antimuscarinics, beta3 agonists have a different profile of side effects and might therefore be beneficial for some patients. The reported dry rates for tolterodine (antimuscarinic) and mirabergron were both around 45%, and therapy adherence was also comparable between both drugs.[39] For the treatment of LUTS attributable to benign prostatic hyperplasia, alpha-blockers still have the most established role, despite new available drug combinations.[40] Pharmacological therapies for other diseases in the field of functional urology, such as UAB and BPS, do not yet have a place within clinical practice. Some large trials are currently investigating pharmacological therapies for UAB and BPS.

Intermittent self-catheterization is a therapy for patients who are unable to void, or have a significant post void residual. The therapy can decrease the risk of renal failure and the amount of urinary tract infections in patients with UAB and is often indicated in neuro-urological patients, to decrease the bladder pressure and to preserve kidney function.[18, 20]

Invasive therapies range from minimally invasive treatments to invasive surgery like the construction of a urinary diversion.

Different minimally-invasive surgical options exist for stress UI, with good results for both women and men.[41, 42] For the treatment of refractory urgency UI, either botulinum toxin A injections or sacral neuromodulation are indicated as minimally-invasive therapies.

Injections with botulinum toxin A is an often-used therapy in patients with neuro-urological disorders. Botulinum toxin A is described to achieve a long-lasting but reversible chemical denervation of the bladder. Possible disadvantages are the need of intermittent catheterization, and the occurrence of urinary tract infections.[43]

Sacral neuromodulation is another option in patients with refractory urgency UI. This implies the placement of an electrode in the sacral foramen alongside a sacral nerve, usually S3. Chronic electrical stimulation of the afferent somatic sacral nerve fibers inhibits the detrusor muscle.[44] The long-term success rates in responders are reported to be 67%.[45] An accurate screening test is necessary to distinguish responders from

non-responders. Patients who have an improvement of at least >50% of symptoms in the test-phase are considered as responders and are candidates for the definitive sacral neuromodulation system. The test phase is currently the only way to select patients for this treatment option; predictive patient characteristics or predictive measurements like urodynamic parameters have not yet been defined.[46, 47] Sacral neuromodulation for neuro-urological patients is thus far not reimbursed, as there is a lack of evidence and it is unclear which patients are most suitable.[48, 49]

Both in non-neuro-urological patients as in neuro-urological patients with UAB or an inability to void, indwelling catheters (suprapubic or urethral) or clean intermittent catheterization can give rise to problems such as urinary tract infections, pain and bleeding. The construction of a continent catheterizable urostoma can be considered. As this is invasive surgery for a non-lethal disease, the risk and benefits have to be considered. A fair comparison is challenging, however, as the literature on the risks of reoperation and complications is scarce.[50]

1.7 AIMS OF THIS THESIS

In general, the aim of this thesis is to investigate potential diagnostic tools in the field of functional urology. This is further specified into two sub aims:

1) To define the brain areas involved in LUT control in healthy individuals and to investigate the clinical applicability of dynamic brain imaging as a diagnostic tool of functional bladder disorders in individuals.
2) To evaluate and improve traditional and patient reported outcome measurements in the field of functional urology.

1.8 OUTLINE OF THIS THESIS

Part I. The use of dynamic brain imaging as potential diagnostic tool within functional urology.

The first part of this thesis is dedicated to the innervation of the LUT and the applicability of dynamic brain imaging as a diagnostic tool in individuals. Firstly, to define the brain areas involved in motor control of the LUT, all evidence on this topic is summarized with a thorough systematic review, including a coordinate-based meta-analysis of all included data (**chapter 2**). In **chapter 3** the central motoric innervation of the LUT is investigated. **Chapter 4** focusses on the sensory innervation of the male genitals. In both chapters 3 and 4, the involved brain areas in the whole brain are identified with the use of 7 Tesla fMRI on both group level and individual level.

Part II. Diagnostics and treatment in functional urology.

As explained above, sacral neuromodulation is an often used therapy for OAB, but we can still not predict who will respond to this therapy and who will not. In **chapter 5**, we investigated whether sacral neuromodulation shows an acute effect on the results of the urodynamic study. We hypothesized, that urodynamics would enable to discriminate between responders and non-responders of sacral neuromodulation directly after implantation. Besides traditional (objective) measurements, the clinical importance of PROMS is increasing, as type and severity of symptoms in patients with OAB can be very heterogeneous. One of the PROMS measuring symptom bother and health-related quality of life in patients with overactive bladder is the OAB-q SF. In **chapter 6**, this questionnaire was translated and validated in Dutch to make it usable in clinical practice in the Netherlands. A selection of patients with LUT disorders do not show improvement on all available minimally invasive treatments. Given the influence of LUT disorders on quality of life, invasive surgery, like the construction of a continent or incontinent urostoma, is sometimes inevitable. In **chapter 7**, the complication rate and reoperation rate of continent catheterizable urinary conduits were measured in all patients undergoing these surgeries in two large academic hospitals in the last 20 years.

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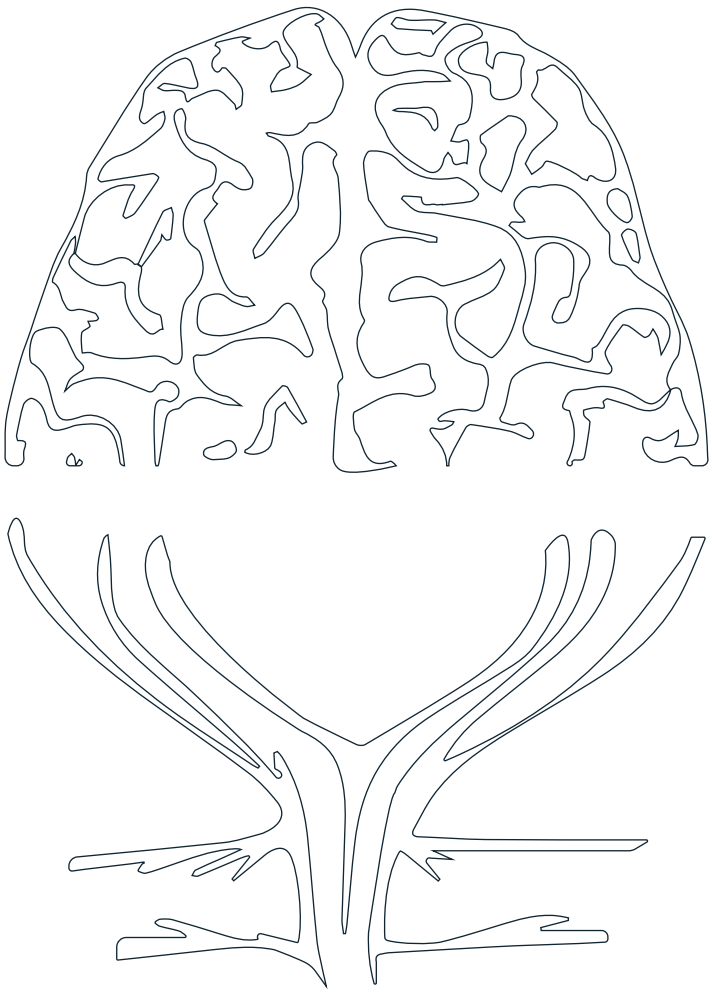
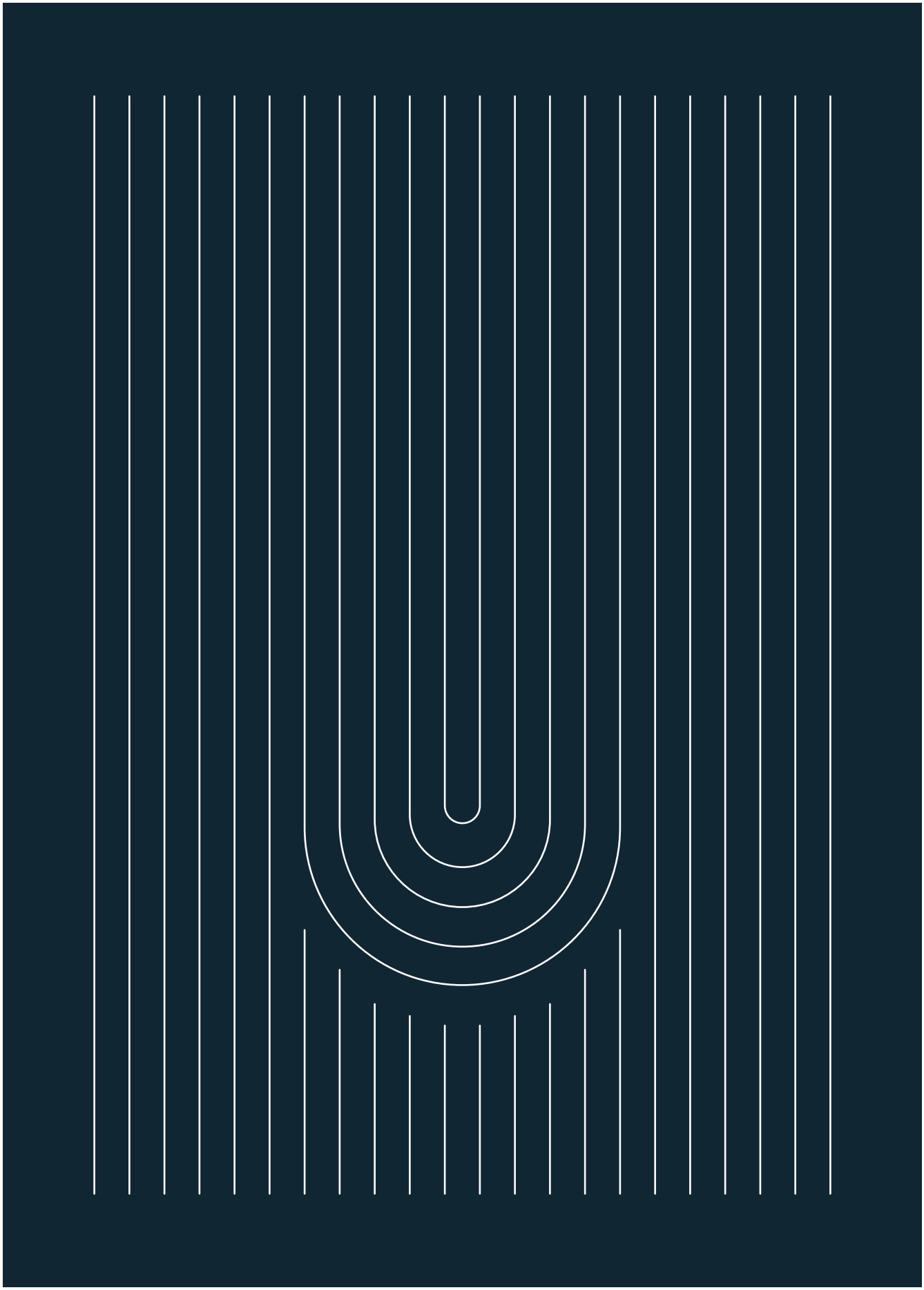


PART I

DYNAMIC BRAIN IMAGING AS POTENTIAL DIAGNOSTIC TOOL IN FUNCTIONAL UROLOGY



CHAPTER 2

A systematic review and activation likelihood estimation meta-analysis of the central innervation of the lower urinary tract: pelvic floor motor control and micturition

Ilse M. Groenendijk*, Ulrich Mehnert*, Jan Groen, Becky D. Clarkson, Jeroen R. Scheepe, Bertil F. M. Blok

* Both authors contributed equally

Submitted for publication

ABSTRACT

Purpose

Functional neuroimaging is a powerful and versatile tool to investigate central lower urinary tract (LUT) control. Despite the increasing body of literature there is a lack of comprehensive overviews on LUT control. Thus, we aimed to execute a coordinate based meta-analysis of all PET and fMRI evidence on descending central LUT control, i.e. pelvic floor muscle contraction (PFMC) and micturition.

Materials and methods

A systematic literature search of all relevant libraries was performed in March 2019. Coordinates of activity were extracted from eligible studies to perform an activation likelihood estimation (ALE) using a threshold of uncorrected $p < 0.001$.

Results

19 of 5718 identified studies, published between 1997 and 2019, were included. Eleven studies investigated PFMC (1xPET, 10xfMRI) and eight micturition (3xPET, 5xfMRI). The PFMC ALE analysis (n=170, 113 foci) showed clusters in the primary motor cortex, supplementary motor cortex, cingulate gyrus, frontal gyrus, thalamus, supramarginal gyrus, and cerebellum. The micturition ALE analysis (n=107, 98 foci) showed active clusters in the pontine micturition center, periaqueductal gray, cingulate gyrus, frontal gyrus, insula and ventral pons. Overlap of PFMC and micturition was found in the cingulate gyrus and thalamus.

Conclusions

For the first time the involved core brain areas of LUT motor control were determined using ALE. Furthermore, the involved brain areas for PFMC and micturition are partially distinct. Further neuroimaging studies are required to extend this ALE analysis and determine the differences between a healthy and a dysfunctional LUT. This requires standardization of protocols and task-execution.

INTRODUCTION

The neuronal control of the lower urinary tract is based on multilevel circuits, i.e. peripheral nerves, autonomic ganglia, spinal cord pathways, and supraspinal centers.[1] The latter allow for the voluntary control and proper coordination of LUT function including synergic micturition (that is, bladder neck and external urethral sphincter relaxation during detrusor contraction).[2-5]

Functional neuroimaging is a powerful and versatile tool to investigate the neural structures and processes involved in central lower urinary tract (LUT) control. The LUT motor control is usually only perceived as storage and micturition, but the descending LUT control includes voluntary pelvic floor muscle contractions (PFMC). Voluntary PFMC are a proxy for, but not the same as, the involuntary tonic contraction employed during the storage phase. Especially since PFMC tends to be a voluntary "backup" mechanism which is employed during very strong urge to void or defecate. Despite the increasing body of literature, publications are scattered among various medical disciplines and there is a lack of comprehensive overview on the descending central LUT control.[2-10] Hence, it would be of great interest to get a structured overview on this topic and determine the most relevant brain areas involved in LUT motor control. This is of importance for a better understanding of the composition of supraspinal LUT control networks and to be able to distinguish between networks involved in healthy control as opposed to LUT dysfunction. This would contribute to elucidate the pathophysiology of some highly prevalent diseases within functional urology, like overactive and underactive bladder (OAB/UAB), bladder pain syndrome (BPS) and dysfunctional voiding.

A well-established approach to conduct a coordinate-based meta-analysis (CBMA) of the existing neuroimaging data in order to achieve a comprehensive overview of the relevant brain regions involved in functional tasks of interest is Activation Likelihood Estimation (ALE) analysis.[11] ALE analyses determine the statistical probability of brain regions being consistently activated during a specific task.

The aim of the present systematic review is to summarize the existing evidence on the supraspinal motor control of the LUT in humans, i.e. micturition and PFMC, and to determine the core brain areas involved in these functions using ALE.

MATERIALS AND METHODS

Study registration

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. The study protocol was registered on PROSPERO (CRD42016047488 https://www.crd.york.ac.uk/PROSPERO/).

Literature search

A systematic search of all relevant publications was conducted in PubMed, EMBASE, Medline, Scopus, Web of Science, and the Cochrane library. A search was conducted including all publications until March 2019, S1 File contains the used search terms. Manual reference checks of accepted papers in recent reviews and included papers were performed as supplement to the electronic search.

Eligibility criteria

All original publications on neuroimaging of lower urinary tract control in humans were eligible for full-text retrieval.

The use of a comprehensive search strategy resulted in a highly heterogeneous body of data which included a variety of neuroimaging techniques, populations, settings and protocols. In order to optimally utilize this extensive literature search, it was decided to split the extracted studies into smaller components addressing more concise research questions to get more precise answers. The current review focused on the assessment of LUT motor control using PET and fMRI.

Hence, inclusion criteria were studies using fMRI or PET when performing micturition or pelvic floor muscle contractions that described the coordinates (in stereotactic space i.e. Talaraich (TAL) or MNI) of active clusters found during the performed task. Duplicates, abstracts only, conference proceedings, non-English text publications, non-human research and reviews were excluded.

Selection of studies

Titles and abstracts were screened in Endnote (EndNote X9; Thomson Reuters, Philadelphia, PA, USA) by U.M. and B.B. and discrepancies were resolved by I.G. The selected articles were full text screened for eligibility by J.G. and I.G. using a standardized screening form, and discrepancies were discussed and resolved by a third reviewer (B.B.).

Data extraction

The data were independently extracted from the included full-text publications by two reviewers (J.G. and I.G.) using a standardized form. Any discrepancies were discussed and resolved by the third reviewer (B.B.). Data extracted were: general descriptive in-

formation of the studies, sample sizes, study population, characteristics describing the scanning protocol, applied analysis and the reported coordinates of supraspinal activity (raw data).

Raw data

The extracted raw data were the coordinates of the activated clusters described by the included studies. The coordinates are shown in the orientation in which they were originally described, i.e. MNI or TAL. Most included studies focusing on micturition, separately reported the coordinates of the patients with successful micturition and unsuccessful micturition. The current study only extracted the coordinates of the subjects with successful micturition if the data was reported separately. In two studies the distinction between successful and unsuccessful micturition was not made.

Primary outcome: Activation Likelihood Estimation (ALE)

Coordinate-based meta-analyses of neuroimaging results were performed using GingerALE software (version 2.3.6) available on the BrainMap website (http://brainmap.org/software.html). ALE analysis uses all the reported foci from the included studies as a spatial probability distribution centered at the given coordinates. The analysis accommodates the spatial uncertainty of neuroimaging findings and uses a spatial variance model. Finally, the convergence of foci is tested against the null-hypothesis of random distribution of foci. The TAL coordinates were converted to MNI space using the icbm2tal transform within the GingerALE software.[12] A lenient threshold was used, taking the amount of data into account (uncorrected p <0.001, minimal volume of 100 mm^3). Results were presented on an MNI template using Mango, multi-image viewing software (http://ric.uthscsa.edu/mango/).

Risk of bias assessment

The Cochrane Risk of Bias Assessment tool together with an assessment of the main confounders following recommendations of the Cochrane handbook for nonrandomized comparative studies[13,14] were used to perform a risk of bias analysis for included nonrandomized comparative studies. Firstly, a manual was developed for scoring the added confounders. Secondly, the main and added confounders were independently scored by two authors (J.G. and I.G.) and discrepancies were discussed. Table 1 shows the used confounders and how they were scored.

Table 1. Scoring manual for the confounders in the risk of bias assessment

Confounders	If yes: low risk If doubtful: unclear risk If not: high risk In case of multiple items in 1 confounder: 1 missing: unclear risk >1 missing: high risk
A priori protocol	Did the authors use and describe a clear protocol?
Age	Did the authors report the age of patients? Is there were different groups to compare, were they age matched?
Gender	Did the authors report the gender of patients? If there were different groups to compare, were they gender matched?
Patient selection	Did the authors clearly state in- and exclusion criteria? Which LUT symptoms and/or dysfunctions had included patients? Were handedness and concomitant medications reported?
Task and scan paradigm	Did the authors report on the task they investigated and how this task was applied (mode of bladder filling, repetition of task, control task, scanning sequence)?
Recording details and scan parameters/settings	Did the authors report all parameters/settings used for the recordings of supraspinal signals? (fMRI: TR, TE, FoV, ST) (PET: camera position, GBq, start time after injection, repeat injection, voxel size)
Data analysis	Did the authors report on data analysis (software, version, analysis steps, smoothing)?
Results	Did the authors report on all result details (coordinated in MNI or Talairach, cluster size of supraspinal areas, z-score, significance lever, error correction) ?

RESULTS

The PRISMA flow diagram in Fig 1 shows the results of the literature search and the study selection. The initially conducted search resulted in 5718 articles. After removing duplicates and title and abstract screening, 151 articles remained for full-text selection and in total 19 studies were included in this systematic review.

Study characteristics

Tables 2 and 3 show the study characteristics of the included studies using fMRI and PET, respectively. The following information was included in Tables 2 and 3: number of subjects, age, gender, performed task, concomitant/control task, task repetition, bladder status, way of bladder filling, scan details and analysis details (smoothing, MNI/TAL, threshold).

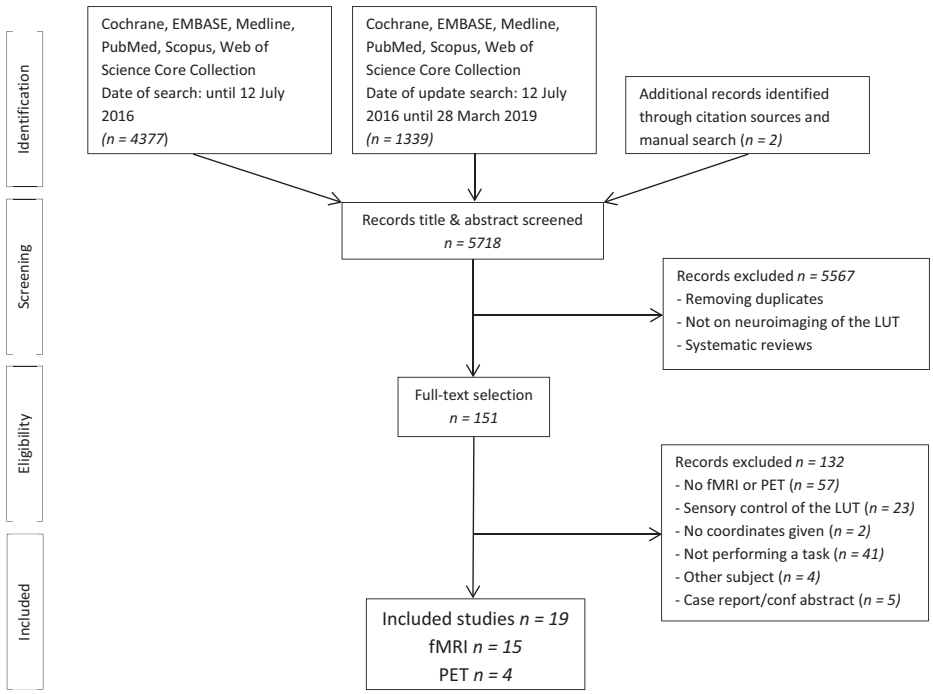


Figure 1. The PRISMA flow diagram

Raw data

Pelvic floor muscle contraction

Eleven studies investigated active brain areas during PFMC. One of them[3] did this using PET, the others all used fMRI.

Of these 11 studies, 8 found active clusters in the primary motor cortex (M1), either in the right or left hemicortex, or both. Six studies found activation in the supplementary motor area (SMA). Some studies reported activation in the frontal lobe, with coordinates widespread through the frontal lobe. The putamen, the thalamus and the insula showed active clusters in 5 studies. Active clusters in the cerebellum were described in 8 studies. S1 Table shows the coordinates of all brain areas that have been consistently found in at least 3 of the included studies. If, in a single study, more than one cluster was identified in the same brain area, the cluster with the highest T- or Z-value is displayed in S1 Table. All active clusters described in individual studies only, are summarized in S2 Table.

Table 2. Study characteristics of fMRI studies.

Main study details					Task paradigm							Scan details and analysis					
Study	N	Healthy volunteers?	Age	M/F	Main task	Concomi-tant tasks	Control task	Design: Block or event related	Main task repetition	Bladder status	Bladder filling	Tesla	-TR -TE -FoV -ST	Software	Smooth Gaussian	Group analyses model	MNI or TAL	Threshold P value
PELVIC FLOOR MUSCLE CONTRACTION																		
Groenendijk, I.M. et al (2020)	13	Healthy volunteers	29.6	13/0	PFMC	None	Tongue movement	Block	12	Empty	-	7T	- 2000 - 25 - 223 - 1.75	SPM8	2.5 mm	Random effects	MNI	Uncorrected <0.001
Kutch, J.J. et al (2015)	14	Healthy volunteers	-	14/0	PFMC	None	Right hand contraction	Block	6	Empty	-	3T	- 2500 - 34.5 - 220 - 3	FMRIB	5 mm	Mixed effects	MNI	Cluster based cor <0.05
Krhut, J. et al (2014)	23	Healthy volunteers	20-68	0/23	PFMC	None	None	Block	10	Unknown	-	3T	- 2000 - 20 - 192 -	SPM8	6 mm	Random effects	MNI	Uncorrected P = 0.0001
Schrum, A. et al (2011)	17	Healthy volunteers	28.9	17/0	PFMC	None	Toe movement	Block	6 fast 6 slow	Empty	-	3T	- 2500 - 34.5 - 224 - 3	SPM5	6 mm	Random effects	MNI	FWE corrected <0.05
Seseke, S. et al (2008)	12	Healthy volunteers	32.4	12/0	PFMC	None	Rest	Block	15	Full	Natural	3T	- 2000 - 36 - - 4	Brain voyager QX	8 mm	Random effects	TAL	FDR <0.05
Kuhtz-Buschbeck, J.P. et al (2007)	30	Healthy volunteers	26.6	15/15	PFMC	None	Rest	Block	5	Variable within subjects	-	1.5T	- - 50 - 220 - 3	SPM2	7 mm	Random effects	MNI	FWE p = variable
Seseke, S. et al (2006)	11	Healthy volunteers	30	0/11	PFMC	None	Rest	Block	15	Full	Natural	3T	- 2000 - 36 - - 4	Brain voyager QX	4 mm	Random effects	TAL	FDR <0.05
Di Gangi Herms, A.M.R. et al (2006)	10	Stress urinary incontinence	57	0/10	PFMC	Pressure balloon in vagina	Fist clenching	Block	11	Empty	-	3T	- 3000 - 30 - - 3	SPM2	9 mm	-	MNI	Corrected <0.05

Table 2. Study characteristics of fMRI studies. (continued)

Main study details					Task paradigm							Scan details and analysis					
Study	**N**	**Healthy volunteers?**	**Age**	**M/F**	**Main task**	**Concomi-tant tasks**	**Control task**	**Design: Block or event related**	**Main task repetition**	**Bladder status**	**Bladder filling**	**Tesla**	**-TR -TE -FoV -ST**	**Software**	**Smooth Gaussian**	**Group analyses model**	**MNI or TAL**	**Threshold P value**
Kuhtz-Buschbeck, J.P. et al (2005)	22	Healthy volunteers	24.5	0/22	PFMC	Initiate micturition, but not void	Rest	Block	5	Full (±300cc)	Natural	1.5T	- - 50 - 220 - 3	SPM2	7 mm	Random effects	MNI	Corrected p= variable
Zhang, H. et al (2005)	12	Healthy volunteers	23.8	12/0	PFMC	None	PFMC with empty bladder	Block	8	Full vs empty	Natural	3T	- 2900 - 30 - 230 - 5	SPM99	8 mm	Conjunction group analysis	TAL	Corrected P = variable
MICTURITION																		
Khavari, R. et al (2017)	16[a]	Multiple sclerosis	46.8	0/16	Initiated micturition	None	Healthy controls	Event related	4	Full	Catheter	3T	- 3000 - 35 - 240 - 4	AFNI	5 mm	-	MNI	P = 0.05
Michels, L. et al (2015)	14[b]	Healthy volunteers	26.4	14/0	Micturition	None	Rest	Event related	10	Full	Natural	3T	- 3000 - 35 - 220 - 3	SPM5	8 mm	Random effects	MNI	FDR P = 0.001
Shy, M. et al (2014)	10	Healthy volunteers	32.4	0/10	Micturition	None	Rest	Event related	4	Full	Catheter	3T	- 3000 - - - 4	AFNI	-	-	MNI	Uncorrected P = 0.00027
Krhut, J. et al (2012)	6[c]	Healthy volunteers	49.6	0/6	Micturition	None	None	Event related	3	Full	Catheter	3T	- 3000 - 30 - - 3	SPM5	8 mm	-	MNI	Uncorrected P = 0.02
Kuhtz-Buschbeck, J.P et al (2009)	33	Healthy volunteers	26.4	16/17	Initiated micturition, but not void	None	Different bladder volumes	Block	5	Full	Natural	1.5T	- - 50 - 220 - 3	SPM2		Random effects	MNI	FWE P = variable

Abbreviations: TR: Repetition time, TE: time of echo, FoV: Field of View, St: Slice thickness, TAL: talairach, PFMC: Pelvic floor muscle contraction.

[a] Of 16 patients, 7 performed successful micturition but data was not reported separately.

[b] Originally 22 patients were included but only 14 performed successful micturition and data was reported separately

[c] Originally 12 patients were included but only 6 performed successful micturition and data was reported separately

Table 3. Study characteristics of PET studies. Abbreviations: GBq: the amount of gigabecquerel H215O (in case of Blok et al diluted in saline) injected before PET scan. TAL: Talairach.

Main study details						Task paradigm						Scan details and analysis						
Study	N	Healthy volunteers = HV	Age	M/F	Main task	Concomitant tasks	Control task	Main task repeti-tion	Design: Block or event related	Bladder status	Bladder filling	camera position -below -above	- GBq - start scan after injection - data acquisition - repeat injection - voxel size	Software	Smooth Gaussian	Group analyses model	MNI or TAL	Threshold P value
PELVIC FLOOR MUSCLE CONTRACTION																		
Blok B.F.M. et al (1997)	6	HV	21 - 24	0/6	PFMC	None	rest	1	Block	empty	-	- -20 - 76	- 1.85 -23 sec - 90 sec -4 -2.2	SPM96	12	ANCOVA	Tal	Uncorrected <0.001
MICTURITION																		
Nour S. et al (2000)	8[a]	HV	23.4 ± 1.1 (22 – 25)	8/0	Micturition	None	rest	2 - 4	Event related	filled to desire	Catheter	- -	- 0.4 - 30 sec - 90 sec - 10 – 12 -	SPM96	10	-	Tal	variable
Blok, B.F.M. et al (1998)	10[b]	HV	27 (20-51)	0/10	Micturition	None	Empty bladder	1	Block	full	Natural	- 28 mm - 48 mm	- 1.85 - 23 sec - 90 sec - 4 - 2.2	SPM95	8	ANCOVA	Tal	Uncorrected <0.001
Blok B.F.M. et al (1997)	10[c]	HV	32.3 (21-50)	10/0	Micturition	None	Empty bladder	1	Block	full	Natural	-28 mm -44 mm	- 1.85 - 23 sec - 90 sec - 4 - 2.2	SPM95	8	ANCOVA	Tal	Uncorrected P = variable

[a] 12 patients were included but only 8 performed successful micturition
[b] 18 patients were included but only 10 performed successful micturition
[c] 17 patients were included but only 10 performed successful micturition

Micturition

Eight studies investigated brain areas involved in micturition, of which 5 used fMRI and 3 used PET. The study of Kuhtz-Buschbeck et al. 2009, investigated initiation of voiding only, i.e. participants prevented voiding by contracting the pelvic floor when micturition was about to start, all other studies investigated real micturition. Only in the study of Khavari et al. data of patients with successful micturition (n=7) and unsuccessful micturition (n=9) were not reported separately. In four studies, patients could sign (hand or vocally) when they were about to start micturition.[15-18] Two studies used a flow/urine detector to detect the start of micturition [5,6] and in two studies patients were instructed when to start micturition.[2,4] Six studies found activation in the periaqueductal gray (PAG) and 5 in the pontine micturition center (PMC). Cingulate gyrus was active in 6 studies. The insula, the thalamus, the mid frontal gyrus and the cerebellum were activated in 4 studies. The inferior frontal gyrus (Brodmann area 11, 44 – 47) was found active in all studies. S3 Table shows peak coordinates of brain areas that were reported to be active in at least 3 of the included studies. If, in a single study, more than one cluster was found in the same brain area, the cluster with the highest T- or Z-value is displayed in S3 Table. All other active clusters described in individual studies only, are summarized in S4 Table.

Primary outcome: Activation Likelihood Estimation

Pelvic floor muscle contraction

The ALE analysis of 113 peak coordinates derived from 11 different studies with a total number of 170 subjects of which 71 men and 87 women (all cluster/peak coordinates summarized in S1 and S2 Tables) yielded 10 active clusters using a statistical threshold of $p = 0.001$ uncorrected with a minimal cluster size of 100 mm^3 (Table 4). Fig 2 displays several of the ALE clusters: primary motor cortex, SMA, cingulate gyrus, insula, thalamus, substantia nigra/red nucleus and the cerebellum.

Micturition

The ALE analyses of 98 peak coordinates derived from 8 different studies with a total number of 107 subjects of which 48 men and 59 women (all peak coordinates summarized in S3 and S4 Tables) yielded 7 active clusters using a statistical threshold of $p = 0.001$ uncorrected with a minimal cluster size of 100 mm^3 (Table 4). Fig 3 displays exemplarily several of the ALE clusters: PMC, PAG, thalamus, cingulate gyrus, frontal gyrus and insula. Cluster 1 shows peak activations in the thalamus, PMC and PAG, but is also situated in the cerebellum.

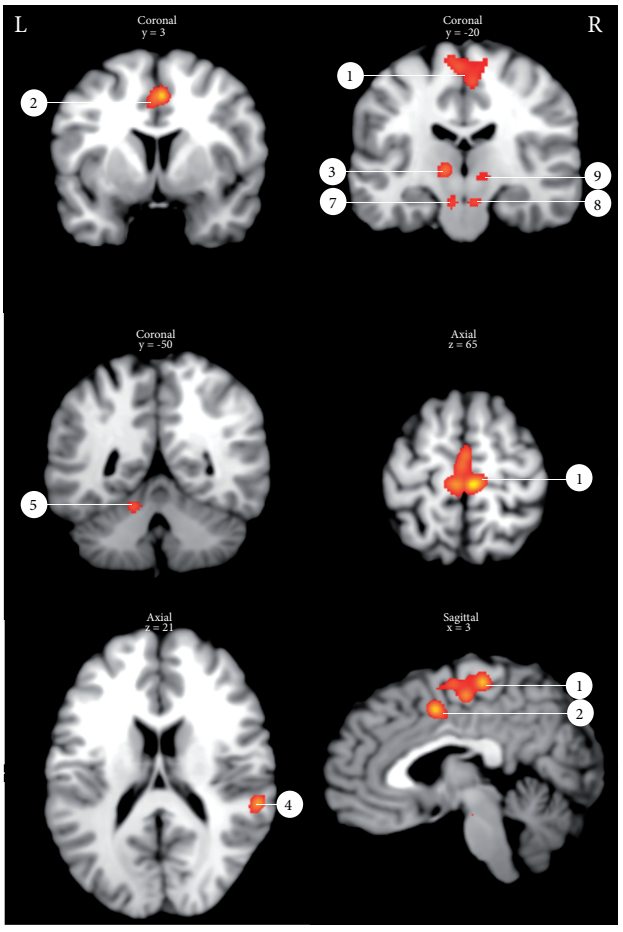


Figure 2. Results of the ALE analysis pelvic floor muscle contraction (p = 0.001 uncorrected with a minimal cluster size of 100m^3). 1: Primary motor cortex & Supplementary motor area, 2: Mid cingulate Gyrus, 3: Thalamus left, 4: Supramarginal gyrus, 5: Cerebellum left, 6: Inferior frontal gyrus, 7: Substantia nigra, 8: Red nucleus, 9: Thalamus right, 10: Posterior superior temporal gyrus.

Overlap

When the results of the ALE analysis of both PFMC and micturition are displayed on the same MNI brain, two clusters show overlap: the cluster in the mid cingulate gyrus (in both figures cluster #2) and the cluster in the left thalamus (in fig 2 PFMC cluster #3 and in fig 3 micturition cluster #1$^{a/d}$). S1 Figure demonstrates the overlap of clusters.

Risk of bias assessment

The results of the risk of bias assessment by the Cochrane Risk of Bias Assessment Tool with confounding factors are shown in fig 4.

Table 4: ALE results of PFMC and micturition tasks. Numbers of clusters correspond with numbers in figures 2 and 3.

Cluster	x	y	z	ALE	R/L	Label
Pelvic floor muscle contraction						
1	6	-26	66	0.024029579	R	Primary motor cortex (BA 4)
1	4	-16	58	0.017922753	R	Supplementary motor area (BA 6)
1	-6	-26	66	0.017806701	L	Primary motor cortex (Ba 4)
1	-2	-14	66	0.016178703	L	Supplementary motor area (BA 6)
1	0	-8	66	0.015730955	L	Supplementary motor area (BA 6)
1	-8	-10	74	0.014048412	L	Supplementary motor are (BA 6)
2	2	4	50	0.020907918		Mid cingulate gyrus (BA6)
3	-12	-16	6	0.017822513	L	Thalamus (BA 50)
4	60	-34	22	0.018866712	R	Insula (BA 13)
5	-14	-50	-14	0.012372754	L	Cerebellum, Anterior Lobe
6	60	12	0	0.012290734	R	Inferior frontal gyrus, pars opercularis (BA 44)
7	-8	-20	-16	0.011285471	L	Brainstem, Substania Nigra
8	6	-20	-16	0.011667801	R	Brainstem, Red Nucleus
9	12	-20	0	0.009602174	R	Thalamus (BA 50)
10	52	12	-8	0.009869569	R	Posterior superior temproral gyrus (BA22)
Micturition						
1[a]	-6	-24	2	0.014630636	L	Thalamus (BA 50)
1[b]	8	-32	-22	0.013637082		Pontine micturition center
1[c]	-2	-30	-8	0.012890372		Periaquatuctal grey
1[d]	-6	-14	-4	0.010864062	L	Thalamus (BA 50)
2	-2	4	44	0.011646116		Cingulate Gyrus (BA 6)
3	-30	32	36	0.009706984	L	Middle Frontal Gyrus (BA 9)
3	-30	42	38	0.009270421	L	Middle Frontal Gyrus (BA 9)
4	38	34	6	0.013441784	R	Insula (BA 13)
5	4	24	48	0.01143695		Superior Frontal Gyrus (BA 8)
6	0	-14	-24	0.009587356		Ventral pons
7	-58	6	4	0.0091044	L	Inferior frontal gyrus, pars opercularis (BA 44)

DISCUSSION

This systematic review and meta-analysis provide a unique overview on the supraspinal areas involved in LUT motor control (pelvic floor muscle contraction and micturition), showing raw data of the acquired PET and fMRI evidence of the past three decades. Furthermore, ALE-analysis enabled us to extract from all raw data across studies the most commonly and reproducibly activated supraspinal areas involved in LUT motor control.

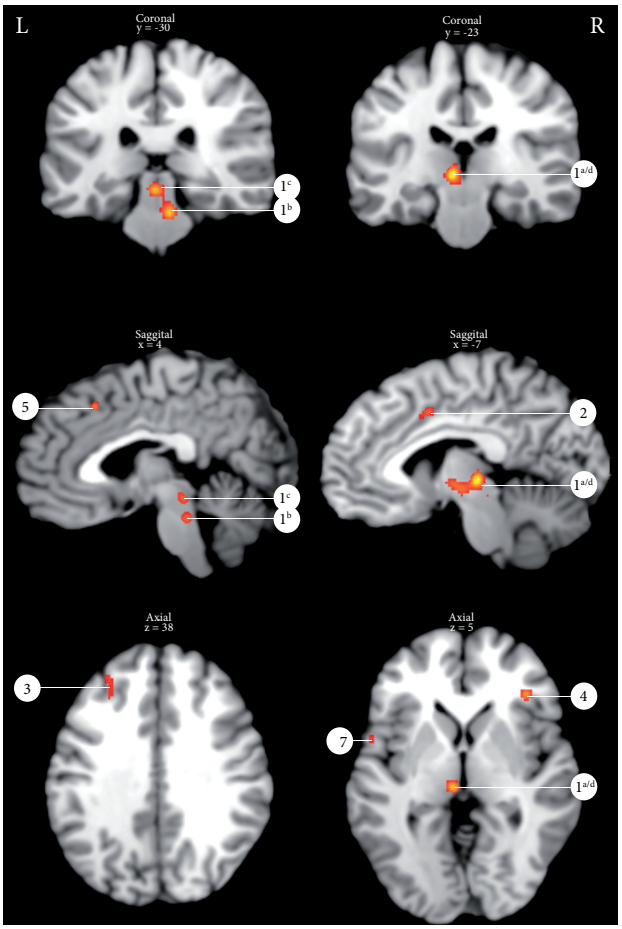


Figure 3. Results of the ALE analysis micturition (p = 0.001 uncorrected with a minimal cluster size of 100m^3). 1$^{a/d}$: Thalamus, 1^2: Pontine micturition center, 1^c: Periaqueductal gray, 2: Cingulate gyrus, 3: Middle frontal gyrus, 4: Insula, 5: Superior frontal gyrus, 6: Ventral pons, 7: Inferior frontal gyrus.

Pelvic floor muscle contraction

S1 Table shows that most studies found active clusters in some obvious brain areas involved in pelvic floor motor control, e.g. M1 and SMA. Unexpectedly, three of the studies did not find activation in the M1[10,19,20] and 5 studies did not find activation in the SMA,[3,21-23] but all studies found activation in either M1 or SMA. Schrum et al. did not find activation in M1. They used a cytoarchitectonic map[24] to detect that more than 80% of the active cluster found in the medial wall belonged to the SMA. The authors argued that activation in the M1 would have been detected using a more liberal threshold.[20] Several human and non-human primate studies have revealed a somatotopic organization of the SMA,[25-27] and showed that the activated areas of the face, the upper limb, and the lower limb were located from anterior to posterior, respectively. This would indicate that activation

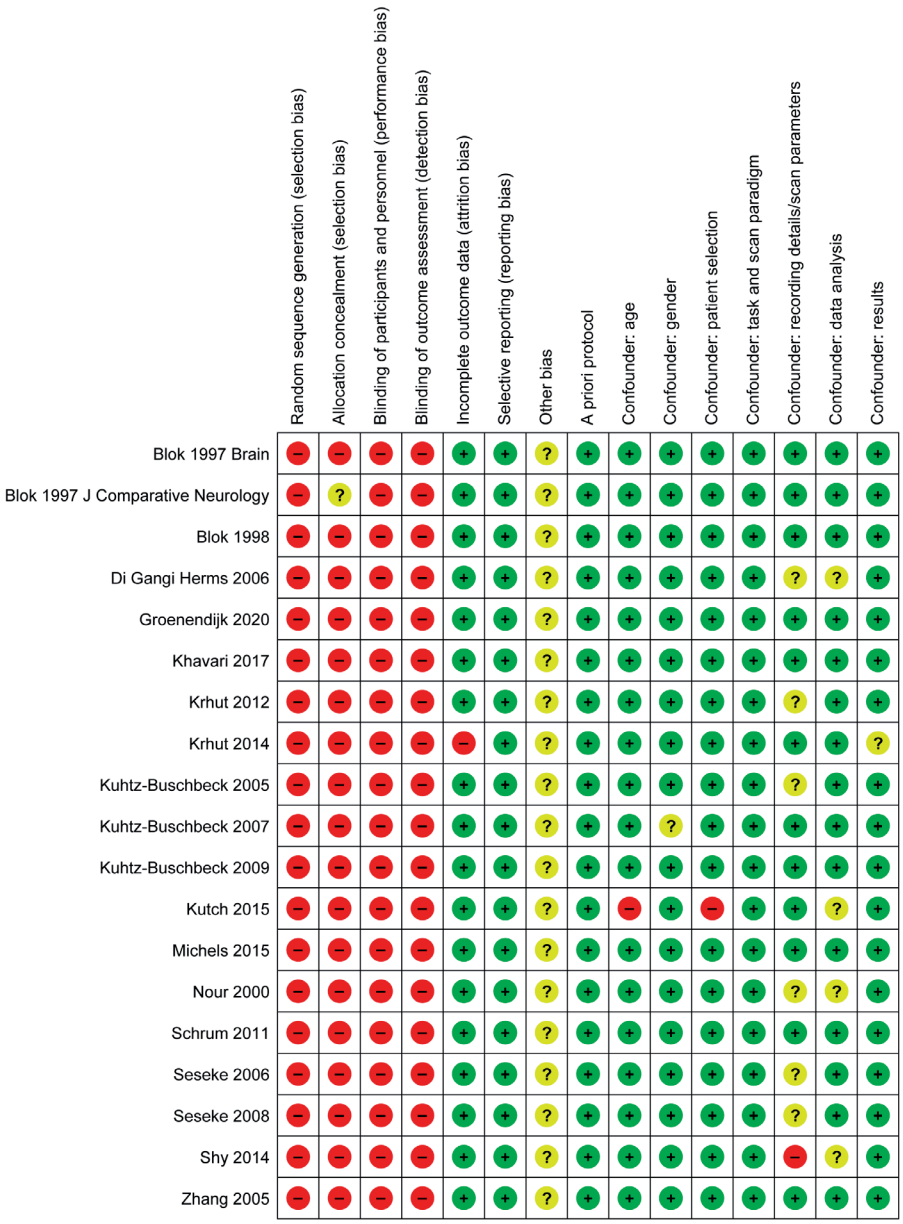


Figure 4. The results of the risk of bias assessment

in the SMA during PFMC might lie in the posterior part of the SMA, which is close to the somatotopic location of activation in the primary motor cortex during PFMC. Furthermore, Di Gangi Herms et al. showed that, after a training interval of 12 weeks regular PFMCs, the number of activated voxels on the SMA decreased significantly compared to before PFMCs training.[28] This demonstrated that the SMA plays an important role in unconditioned motor tasks, like PFMC. Thus, PFMC being an unconditioned task might induce the appearance of large clusters on SMA, and together with its orientation in the posterior SMA, these clusters might be indistinguishable from activation in M1. This could be an explanation for the incongruent findings of the different studies on M1 or SMA.

To our knowledge, our study is the first to confirm the involved brain areas in pelvic floor motor control using an ALE-analysis (Fig 2), namely the: M1, SMA, prefrontal cortex (BA 6 & 9), cingulate gyrus, thalamus, supramarginal gyrus and the anterior lobe of the cerebellum. Putamen activation however, was found in 4 of the included studies,[10,20,23,29] but not in our ALE analysis. A possible explanation might be that the coordinates of the peak activations are spread across the putamen and that this did not result in the formation of a cluster in the ALE analysis. The role of the putamen in LUT control has been confirmed earlier, as this structure plays an important role in the corticostriatal pathway which participates in motor action selection and coordination.[30]

The ALE analysis revealed two clusters (#7 and #8) covering the substantia nigra and the red nucleus: parts of the basal ganglia involved in motor tasks.[31] Two studies contributed to the formation of these clusters in the ALE analysis.[20,22]

Micturition

Micturition is a complex process, involving both voluntary and involuntary control regulated by a supraspinal network. Until 1996, all available evidence for supraspinal micturition control was obtained from animal studies in cats[32] or from case reports of humans with lesions in the prefrontal cortex.[33] Blok et al. were the first to show brain activation in humans during micturition using PET.[2,6] However, the evidence in humans is still limited, possibly due to the fact that this LUT motor task is complicated to study. This is caused by several reasons; 1) In case of BOLD fMRI, repeated captures of the event-related data are necessary to obtain a higher signal-to-noise ratio, which is hard to establish considering the complex (autonomic and somatic) control of micturition, 2) Involved brain areas lie relatively closely to each other in the brainstem (PMC/PAG/thalamus); distinguishing these areas requires high resolution imaging, 3) A significant number of subjects are not able to void in the scanner, possibly due to the involvement of the prefrontal cortex involved in decision making in social context.[1] The current study describes all PET and fMRI evidence for supraspinal micturition control and included 8 studies with a total of 107 subjects. S3 Table shows all raw data obtained in the last three decades. Using ALE analysis, this study evaluated all evidence

and confirmed the involvement of these key brain areas during micturition: the PMC, the PAG, thalamus, cingulate gyrus, prefrontal cortex, the insula and the cerebellum. Cluster 1 is a merged cluster covering the thalamus, PAG, PMC and the cerebellum. It has three obvious peak activations in the thalamus, PAG and PMC as shown in Fig 3. These current findings are in line with previous working models on the supraspinal networks supposed to be involved in micturition.[1]

S3 and S4 Tables show that all studies found multiple active clusters diffuse across the prefrontal cortex. Peak activations were found in all Brodmann areas within the prefrontal cortex, most of which were located in Brodmann areas 9 and 44. Both areas (the medial prefrontal cortex and the inferior frontal cortex) have been described previously to be involved in micturition.[34,35] The variability of the exact activity location within these areas may result from the variety of different protocols applied in the included studies. The prefrontal cortex has strong connections with other limbic structures – the hypothalamus, amygdala, insula and cingulate gyrus and is known to be involved in the planning of complex cognitive behavior and appropriate social behavior.[36] The voluntary decision when to void is generated in the prefrontal cortex in turn sending efferent signals via the cingulate to the PAG and PMC.[1] The ALE analysis did not show an active cluster in the hypothalamus. However, two of the included studies did find such a cluster as shown in S4 Table.[2,6] As the hypothalamus is part of the limbic system, its role in micturition has been described before.[37] The size of the area is rather small, making detection of active clusters challenging.

Micturition vs PFMC

This systematic review studies the motor control of the LUT, consisting of one voluntary controlled task (PFMC) and one semi-voluntary controlled task (micturition). Although PFMC and micturition are both motor tasks of the LUT, they have completely different goals. Micturition is a complex coordinated process between the urinary bladder and the external urethral sphincter that aims to empty the bladder periodically, whereas PFMC is a more confined motor task. PFMC concerns the voluntary (M1) contraction on top of the involuntary tonic contraction of the urethral sphincter, which is responsible for urinary continence. The minimal overlap of activated brain areas was therefore expected and demonstrates this distinct working mechanism of the supraspinal organization of both tasks. Comparison of the results shows that only two clusters overlap: midcingulate gyrus (MCG) and the left thalamus. The important role of the MCG in reward-based decision making has been described before,[38] and involvement of this area was expected in both LUT motor tasks. The involvement of the basal ganglia was also expected in both tasks. The thalamocortical pathway is important in execution of motor tasks.[39] But, the thalamus is also involved in interoceptive networks, and is therefore important in initiation of micturition.[5]

PFMC can be studied during different bladder states (empty vs full), sometimes used to interrupt micturition or suppress the urge to void. In the PFMC ALE, 4 studies investigated PFMC with a full bladder.[10,19,22,23] Among those, Zhang et al. compared activation between PFMC with empty vs full bladder and demonstrated differences in SMA, basal ganglia and cerebellum. This might be of great interest towards the clinical applicability of fMRI in patient populations. To better understand the influence of bladder status on pelvic floor control, further studies comparing results at different bladder states are necessary.

Although the current meta-analysis did not specifically focus on sex related differences, data of both men and women were included. Tables 2 and 3 demonstrate that only two studies (1 PFMC and 1 micturition) in this review studied both men and women.[4,7] The amount of data in the current systematic review was not sufficient to repeat the ALE analysis separately for men and women to study differences. The studies that included both men and women did compare the results between men and women. Moreover, the study of Seseke et al. focused specifically on this topic in relation to micturition comparing their male results with previous female results.[22] In PFMC, no sex related differences were found,[7] however, in another study about external anal sphincter contraction, greater activity was found in men.[40] Various arguments for this difference are described, like a more forceful contraction in men, the obvious anatomical differences between the genitourinary system or a general interhemispheric asymmetry of the human motor cortex related to sexes.[7,40,41] In micturition, stronger task related activity in the right thalamus and other right-hemispherical regions was found in women compared to men.[4] Still, results on this topic are scarce and very heterogeneous. Other studies speculate that women have a stronger brain activity during visceral stimulation than men.[42,43]

Clinical implications & reliability

Since our knowledge about the physiology of the innervation of the LUT has grown, lately more research is focusing on the results of neuroimaging in patients with LUT disorders, like chronic pelvic pain syndrome,[21] stress urinary incontinence (SUI),[28] urge urinary incontinence[44,45] or multiple sclerosis (MS).[15,46] Khavari et al.,[46] studied differences in activation after onabotulinumA injections in patients with UUI and MS compared to healthy controls. It was demonstrated that during full urge, patients with UUI and MS show more deactivations compared to healthy controls in cortical and subcortical structures. After onabotulinumA injections, the brain responses were more in agreement with those of healthy controls. Furthermore, a study of Griffiths et al.[45] clearly demonstrated an increased activation in patients with full bladder and UUI compared to healthy controls, particularly in the cingulate gyrus, SMA and prefrontal cortex. What these studies suggest, is that when patients react to therapy, activation patterns had more similarities with those of healthy controls, which is a very usable finding in future implication of fMRI.[10,15,28,45-47] In the current ALE analysis, two studies were included with

a patient population instead of healthy controls. One micturition related study included patients with MS[15] and one PFMC related study included patients with SUI.[28] Both ALE analyses (PFMC and micturition) were repeated without inclusion of the patient data to assess the influence on the outcome. Only the amount of clusters changed (the ones with the lowest ALE values disappeared), however, most probably due to the lower number of included subjects in the ALE analysis which is critical for the validity of such analysis and hampers a reasonable interpretation of these differences from a statistical point of view. As visible in the raw data in the supplements, both studies including patient data do not show remarkable outliers, or other distinguishing results compared to the studies including healthy volunteers.

Studying differences in activation patterns between healthy controls and patients is important for future clinical implications of neuroimaging and the search towards finding the pathophysiology of diseases within functional urology. The SMA, cingulate gyrus and prefrontal cortex have been independently described as areas of interest when evaluating differences between patients and healthy controls, full or empty bladder and effect of therapies.[10,15,28,45-47]

ALE analysis highlights consistently involved brain areas during the execution of both tasks, however, not every included study found the same main core areas. This poor reliability or reproducibility might be the cause of the limited clinical translatability of functional neuroimaging findings. Recently, two studies investigated the reliability of functional neuroimaging of the LUT.[48,49] Both studies investigated the reliability with bladder-filling protocols, rather than the motor control addressed here, and detected a moderate reliability with maximum inter-class correlation coefficients of 0.44[48] and 0.55.[49] Several reasons for this poor reliability can be suggested like inhomogeneous patient groups, small patient groups, inconsistent task execution or habituation to tasks. In addition, the strong involvement of psychological factors in performing LUT motor tasks may considerably contribute to the variability of results, not only between subjects but also within a given subject over time. Hence, reliability requires improvement. Two aspects appear relevant for this endeavor: a) validation of task and recording parameters to better understand and control for measurement related bias and b) correlation of neuroimaging findings to clinical outcomes to better understand the relation between supraspinal activity patterns and dysfunction or symptoms. To better compare between or pool studies, harmonization of protocols and terminology would be of great advantage.[50]

Limitations

The current systematic review and ALE analysis makes all raw data available and creates a clear overview of fMRI and PET imaging of the supraspinal control of the LUT. Our liberal search strategy additionally allowed a very comprehensive review. Nevertheless, there

are limitations. This systematic review only included studies using the neuroimaging techniques fMRI or PET, since these techniques yield reliable coordinated-based results, usable for the ALE analysis. Data of other neuroimaging techniques apart from fMRI and PET was therefore not included. Furthermore, to perform a valid ALE analysis and reach sufficient power, the amount of included data is important, which is a criticizable point in the current ALE analysis.[51] However, within the urological field the amount of neuroimaging data is still limited making the use of a liberal threshold inevitable when performing a coordinate based meta-analysis. Altogether, the results of the current systematic review have to be interpreted with the limited amount of data and the risk of bias in mind. Generating more data on this topic is necessary towards applicability of this technique in clinical practice.

Another limitation is that this review does not focus on deactivations. As most included studies only report activations, it was decided to focus on activation and not on deactivation. Comparing the overlap of the PFMC and micturition task can therefore be partly biased (see S1 Figure). For example, a cluster that activated during PFMC but deactivated during micturition should be counted as an overlapping cluster, but is not found in the current analysis. Despite both tasks are motor tasks of the LUT, they may be used in opposite direction since the pelvic floor should not be contracted during micturition.

The risk of bias analysis was performed using the Cochrane risk of bias guidelines.[14] As this tool is not specifically designed for neuroimaging studies, the risk of bias might be underestimated. It revealed an unclear risk of bias, which is at least partly related to the great variability of study designs, scan protocols, analysis pathways, and the lack of standardization of reporting methods and outcome measures.

Conclusions

This systematic review and ALE analysis define all fMRI and PET evidence for the motoric innervation of the LUT. The key brain areas involved in PFMC are M1, SMA, cingulate gyrus, putamen, thalamus, prefrontal cortex, supramarginal gyrus, insula and the cerebellum. The key brain areas involved in micturition are the PAG, PMC, cingulate gyrus, insula, thalamus, prefrontal cortex and the cerebellum. Considering the presented activations, both, PFMC and micturition appear distinct which is in line with their different contextual execution. However, deactivations which are underreported and less well understood could not be systematically considered and may show more overlap than currently presented. Despite that the evidence for neuroimaging of the LUT is still scarce and the affective involvement in performing these tasks makes it challenging to study LUT motor tasks, the involved brain areas in healthy controls seem to be defined, so the step towards defining pathology in a patient population with functional bladder disorders can be made. However, this requires standardization of protocols and task execution.

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SUPPLEMENTS

#4 #1 AND #2 NOT ([animals]/lim NOT [humans]/lim) NOT [conference abstract]/lim

#3 #1 AND #2

#2
'bladder dysfunction'/exp OR 'urinary dysfunction'/exp OR 'bladder function'/exp OR 'cystometry'/exp OR 'chronic prostatitis'/exp OR 'interstitial cystitis'/exp OR micturition:ab,ti OR (urin* NEAR/3 (control* OR retention OR storage OR urge* OR incontinent* OR void* OR dysfunction OR frequency)):ab,ti OR (bladder NEAR/3 (control* OR sensation OR filling OR storage OR urge* OR incontinent* OR instability OR overactiv* OR distention OR neurogenic OR distention OR task OR void* OR inhibition OR capacity OR contraction OR compliance OR emptying OR volume)):ab,ti OR (detrusor NEAR/3 (instability OR dyssenergia OR overactive* OR underactive*)):ab,ti OR (void* NEAR/3 (control* OR dysfunction* OR pattern OR symptom* PR desire OR pressure)):ab,ti OR ('lower urinary tract'NEAR/3 (symptom* OR dysfunction)):ab,ti OR (pelvic NEAR/3 (pain OR contraction*)):ab,ti OR ('pressure-flow' NEAR/3 stud*):ab,ti OR urodynamic*:ab,ti OR uroflowmetr*:ab,ti OR cystomanometry:ab,ti OR cystometric:ab,ti OR cystometrogram:ab, ti OR cystometrography:ab,ti OR cystotonometry:ab,ti OR 'chronic prostatitis':ab,ti OR 'interstitial cystitis':ab,ti

#1
'functional neuroimaging'/exp OR 'neuroimaging'/exp OR 'positron emission tomography'/exp OR 'functional magnetic resonance imaging'/exp OR 'single photon emission computer tomography'/exp OR 'near infrafed spectroscopy'/exp OR 'voxel based morphometry'/exp OR diffusion tensor imaging'/exp OR 'diffusion weighted imaging'/exp OR 'tractography'/exp OR 'electroencephalography'/exp OR 'magnetoencephalography'/exp OR 'brain mapping'/exp OR neuroimaging:ab,ti OR 'emission computed tomography':ab,ti OR spec:ab,ti OR pet:ab,ti OR fMRI:ab,ti OR vbm:ab,ti OR dti:ab,ti OR rsmri:ab,ti OR tractography:ab,ti OR electroencephalography:ab,ti OR eeg:ab,ti OR magnetoencephalography:ab,ti OR meg:ab,ti OR 'brain mapping':ab,ti OR brainmapping: ab,ti OR 'High definition fiber tracking':de,ab,ti OR 'high-definition fiber tractography:de,ab,ti OR (positron NEAR/3 tomograph*):ab,ti OR (*functional NEAR/3 (mri OR 'magnetic resonance imaging')):ab,ti OR ('near infrared'NEAR/3 spectoscopy):ab,ti OR ('voxel based'NEAR/1 morphometr*):ab,ti OR (('diffusion tensor' OR 'diffusion weighted' OR 'resting state') NEAR/3 (imaging OR mri OR 'magnetic resonance')):ab,ti OR ((electric* OR magnet*) NEAR/3 encephalography):ab,ti OR ('white matter' NEAR/3 hyperintens*):ab,ti

S1 File. Search terms

S1 Table. Peak coordinates of clusters with task specific activity (pelvic floor contraction) in certain brain areas. For purposes of a more concise overview, only brain areas are listed that have been reported to demonstrate task specific activity in at least 3 of the included studies. Further brain areas with task specific activity in individual studies only, are summarized in supplementary 3.

Brain area		**M1**				**SMA**					**Medial frontal gyrus (BA 6/9)**					**Supramarginal gyrus (BA 40)**					**Cingulate gyrus**				
Orientation		**x**	**y**	**z**	***T***	**x**	**y**	**z**	***T***	***Z***	**x**	**y**	**z**	***T***	***Z***	**x**	**y**	**z**	***T***	***Z***	**x**	**y**	**z**	***T***	***Z***
Groenendijk I., 2020	R	12	-24	66	5.8	2	-6	64	7.6																
MNI	L	-12	-26	66	8.7	-2	-16	68	7.6												-4	-6	46	7.6	
Kutch J., 2015	R	4	-26	66																					
MNI	L																								
Kruht J., 2014	R	4	-27	65	10	2	2	50	13	4.9	42	36	32			62	-34	22							
MNI	L	-4	-27	65	10	-2	2	50	13	4.9	-38	36	32												
Schrum A., 2011	R					2	2	62		6.5											-6	6	42		5.8
MNI	L															-56	-32	22		5.8					
Seseke S., 2008	R	6	-32	60	12																1	-49	31	10	
Talairach	L	-7	-31	59	12						-7	50	35	10											
Kuhtz-Buschbeck j., 2007	R					0	-9	66	9							60	-33	21	6.2		0	0	45	7	
MNI	L	-9	-21	72	6	0	-15	57	9																
Seseke S., 2006	R	1	-30	58	10																-7	-42	17	6	
Talairach	L																								
Di Gangi Herms A., 2006	R	15	-21	72	6	3	6	51	7.5	4.1											0	15	42	5	3.4
MNI	L	-3	-15	66	6						-9	-9	72	4.1											
Kuhtz-Buschbeck j., 2005	R					6	-18	57		4.8						57	-39	21		4.2	-6	-6	42		4.3
MNI	L										-9	-9	75		4										
Zhang H., 2005	R					8	-8	62		7.3						64	-18	16		4.3					
Talairach	L																								
Blok B., 1997	R	2	-32	66							30	-20	62		3										
Talairach	L	-6	-26	74																					

Brain area		Putamen					Thalamus					Insula					Cerebellum				
Orientation		**x**	**y**	**z**	***T***	***Z***	**x**	**y**	**z**	***T***	***Z***	**x**	**y**	**z**	***T***	***Z***	**x**	**y**	**z**	***T***	***Z***
Groenendijk I., 2020	R	28	-4	16	9.9		10	-16	-14	4.1		46	4	2	6.1		10	-46	-10	3.9	
MNI	L	-26	0	12	13		-12	-16	6	5.1		-32	0	12	6		-16	-48	-14	5.3	
Kutch J., 2015	R																				
MNI	L																				
Kruht J., 2014	R																				
MNI	L																				
Schrum A., 2011	R	34	2	4		6.3	8	-22	-2		6.1	34	18	2		6.2					
MNI	L	-26	-14	4		5.8	-10	-18	4		5.7	-44	0	-4		7	-4	-58	-32		5
Seseke S., 2008	R						13	-20	3	7.1							19	-54	-17	10	
Talairach	L						-14	-22	3	6.8							-14	-49	-14	9.4	
Kuhtz-Buschbeck j., 2007	R											51	12	-9	6.6		6	-42	-24		
MNI	L																				
Seseke S., 2006	R	30	-18	16	6																
Talairach	L	-29	-18	12	6												-1	-47	-14		
Di Gangi Herms A., 2006	R											57	15	-3	7.3	4.1	0	-75	-12	4.6	3.2
MNI	L																-36	-60	-21	4.4	4.1
Kuhtz-Buschbeck j., 2005	R											45	9	-9		4.4					
MNI	L						-12	-12	9		3.4										
Zhang H., 2005	R	28	6	-2		4.5											18	-32	-10		4.2
Talairach	L	-24	10	-6		4															
Blok B., 1997	R																				
Talairach	L						-10	-4	4		3.2						-6	-52	-12		3.9

S2 Table. Peak coordinates of clusters with task specific activity (pelvic floor muscle contraction), not shown in supplement 2.

		x	y	z	T	Z	Hemisphere	Area
Groenendijk, I.M.	2020 MNI	-48	-2	52	3,3		L	inferolateral M1
		42	-2	54	3,7		R	inferolateral M1
Kutch, J.J.	2015 MNI	All clusters presented in table 3						
Kruht, J.	2014 MNI	43	-13	63	8,2	3,6	L	precentral gyrus
Schrum, A.	2011 MNI	-52	-40	48		5,3	L	posterior parietal cortex
		50	-30	16		6,6	R	patietal operculum
		-8	-20	-18		5,8	L	upper ventral pons
		4	-20	-16		5,3	R	upper ventral pons
Seseke, S.	2008 TAL	-42	-59	15	9,9		L	middle temporal cortex
		24	-83	11	9,2		R	occipital cortex
		-16	-81	15	9,6		L	occipital cortex
		2	-49	-18	9,1		R	vermis
		4	-19	-30	6,2		R	ventral pons
		8	-18	-11	4,6		R	peri-aquaductal grey
		-7	-17	-9	4,6		L	peri-aquaductal grey
Kuhtz-Buschbeck, J.P.	2007 MNI	3	3	48	7,5		R	superior frontal gyrus
		-57	6	0	8,7		L	frontal operculum
		60	12	0	9,2		R	frontal operculum
Seseke, S.	2006 TAL	40	-70	28	5,5		R	occipital cortex
		-36	-69	25	7,1		L	occipital cortex
Di Gangi Herms, A.M.R	2006 MNI	21	-30	69	5,2	3,5	R	superior lateral postcentral gyrus
		-18	-33	72	4,7	3,3	L	superior lateral postcentral gyrus
		-54	3	42	8,56	4,4	L	premotor area
Kuhtz-Buschbeck	2005 MNI	All clusters presented in table 3						
Zhang, H. 2005	2005 TAL	-2	-30	70		5,6	L	paracentral lobule
		4	-78	44		5,3	R	percuneus
		18	-32	-10		4,2	R	parahippocampal gyrus/limbic lobe
		-20	18	6		3,9	L	putamen
		10	-38	68		3,9	R	paracentral lobule
Blok, B.F.M.	1997 TAL	16	30	54		3,7	R	superior frontal gyrus
		24	16	32		3,7	R	medial frontal gyrus
		36	-52	20		3,1	R	temporal lobe
		16	50	14		2,8	R	anterior cingulate and medial frontal gyrus

S3 Table. Peak coordinates of clusters with task specific activity (micturition) in certain brain areas. For purposes of a more concise overview, only brain areas are listed that have been reported to demonstrate task specific activity in at least 3 of the included studies. Further brain areas with task specific activity in individual studies only, are summarized in supplementary 5.

Brain area		**Periaquaductal grey**					**Pons (pontine micturition center)**					**Cingulate gyrus**					**Insula**					**Thalamus**				
Orientation		**x**	**y**	**z**	***T***	***Z***	**x**	**y**	**z**	***T***	***Z***	**x**	**y**	**z**	***T***	***Z***	**x**	**y**	**z**	***T***	***Z***	**x**	**y**	**z**	***T***	***Z***
Khavari R., 2017	R	8	-27	-17	-3.4		0	-13	-23	-4.4		-6	7	44	-4.8											
MNI	L																-45	-3	3	-4.8		-6	-24	1	-4.5	
Michels L., 2015	R	-6	-15	-6	2.9		6	-30	-24	5.5		12	-30	42	5.5		36	18	9	3.3						
MNI	L																-33	24	3	3		-18	-18	6	4.8	
Sky M., 2014	R						0	-16	-30	5.8		-7	14	39	5.8											
MNI	L																					-9	-22	0	5.8	
Kruht J., 2012	R											-10	37	-6	3.6	2.4										
MNI	L																									
Kuhtz-Buschbeck j., 2009	R	-3	-30	-9	2.4	2.3						0	3	45	9	6.3	45	15	-9	7.3	5.6					
MNI	L																-42	12	-3	6.7	5.2					
Nour S., 2000	R	4	-26	-6		5.2						-4	0	46		5	36	4	14		6.2					
Talairach	L																					-4	-24	6		4.9
Blok B., 1998	R	2	-38	-24		2.8	12	-36	-28		3.6															
Talairach	L																									
Blok B., 1997	R	4	-34	-12		3.1	10	-42	-24		2.6															
Talairach	L																									

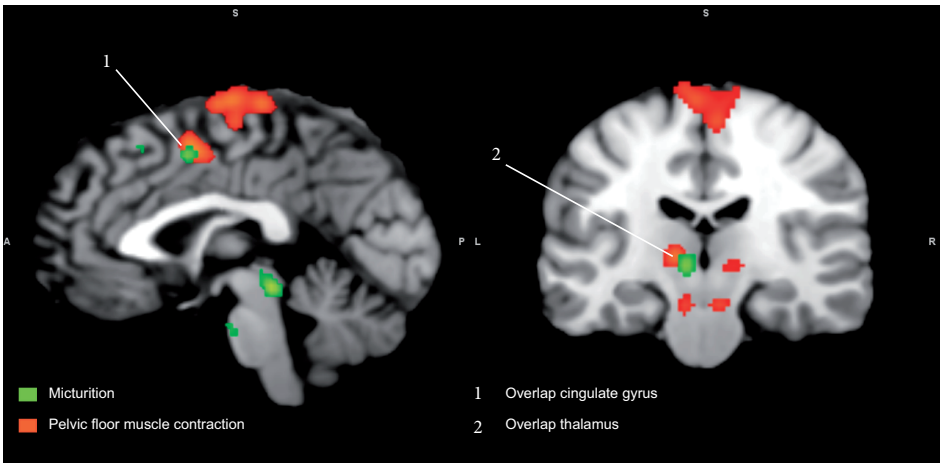
Brain area		Inferior frontal gyrus (BA 11, 44-47)					Mid frontal gyrus (BA 9 or 10)					Cerebellum				
Orientation		**x**	**y**	**z**	***T***	***Z***	**x**	**y**	**z**	***T***	***Z***	**x**	**y**	**z**	***T***	***Z***
Khavari R., 2017	R	38	33	6	-5.2							7	-61	-52	-3.4	
MNI	L	-39	34	5	-3.9		-31	44	39	-3.7						
Michels L., 2015	R	48	45	-6	7.3							30	-57	-45	3.5	
MNI	L	-57	6	14	4.8		-30	30	36	5.3		-42	-51	-39	5.2	
Sky M., 2014	R	40	35	6	5.8											
MNI	L	-47	27	-4	5.8		-28	37	36	5.8		-35	-32	-32	5.8	
Kruht J., 2012	R	11	42	-12	3.6	2.4										
MNI	L	-11	43	-12	3.6	2.4										
Kuhtz-Buschbeck j., 2009	R	60	12	6	6.7	5.2	48	51	6	7.5	5.6					
MNI	L	-57	6	3	8.1	5.9										
Nour S., 2000	R	48	4	10		5.7						30	-42	-50		5
Talairach	L	-66	4	14		5.3						-38	-54	-34		6
Blok B., 1998	R	52	24	12		3.1										
Talairach	L															
Blok B., 1997	R	48	26	-4		4.6										
*Talairac*h	L															

S4 Table. Peak coordinates of clusters with task specific activity (pelvic floor muscle contraction), not shown in supplement 4.

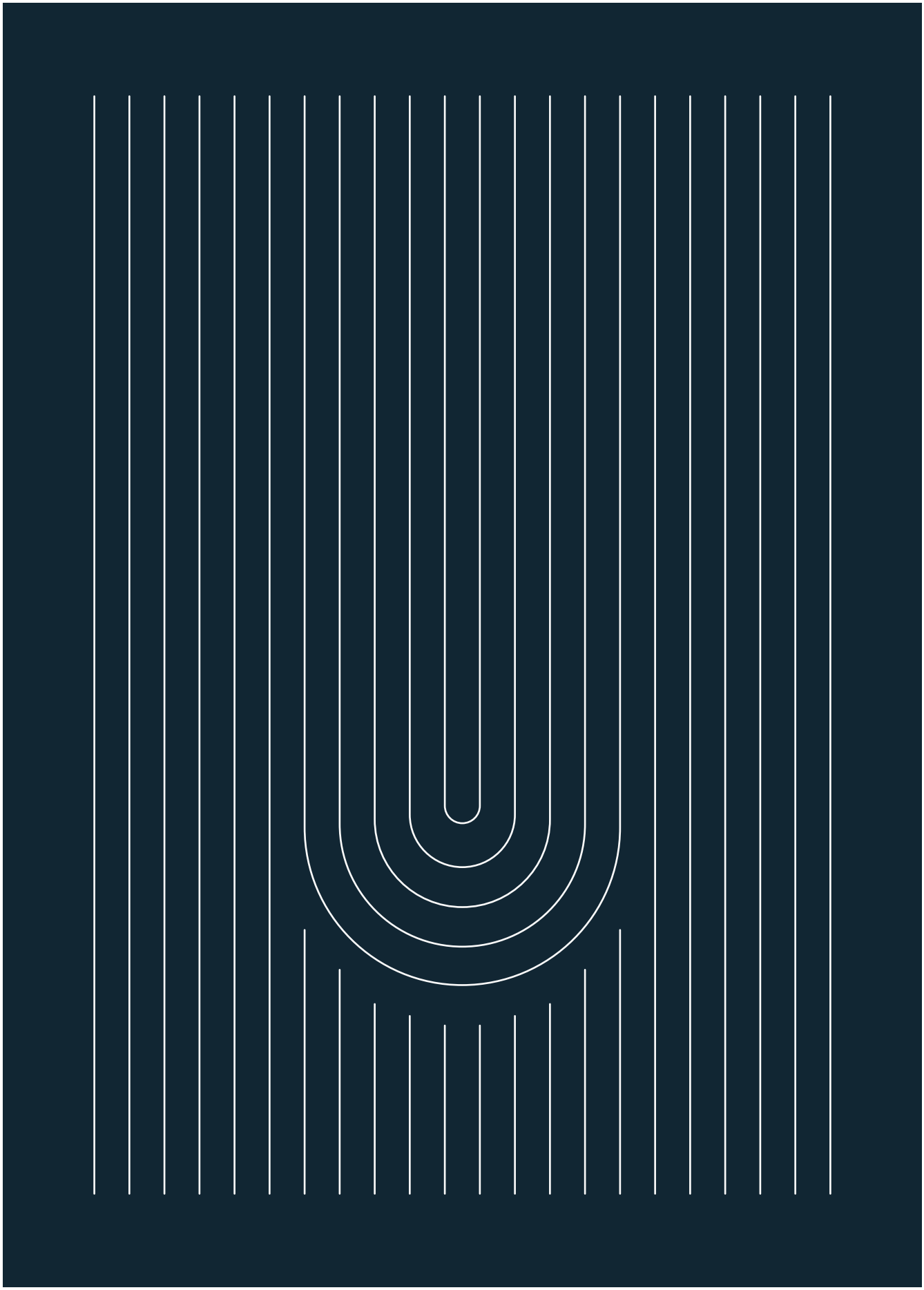
		x	y	z	T	Z	Hemisphere	brain area
Khavari, R.	2017 MNI	-6	-13	15	-3,8		L	thalamus
		0	-29	26	-3,6			cingulate gyrus
Michels, L.	2015 MNI	-57	-27	18	6,7		L	postcentral gyrus
		63	18	18	3,4		R	inferior frontal gyrus
		-51	-63	3	5,4		L	middle temporal gyrus
		62	-18	18	7,2		R	postcentral gyrus
		15	-72	48	4,6		R	percuneus
Shy, M.	2014 MNI	-44	1	28	5,7		L	precentral gyrus
		-19	-9	52	5,7		L	middle frontal gyrus
		-16	17	37	5,7			cingulate gyrus
		21	10	-14	5,7		R	subcalossal gyrus
		8	22	44	5,7		R	cingulate gyrus
		-33	27	30	5,7		L	middle frontal gyrus
		-5	21	47	5,7		L	medial frontal gyrus
		-18	28	52	5,7		L	superior frontal gyrus
		-32	-11	47	5,7		L	middle frontal gyrus
		-42	33	26	5,7		L	middle frontal gyrus
		-32	12	33	5,7		L	middle frontal gyrus
Krhut, J.	2012 MNI	-16	-39	-7	4,9	2,9	L	parahippocampal gyrus
		10	37	-6	3,6	2,4	R	cingulate gyrus
		-56	-50	-10	4,9	2,9	L	temporal gyrus/inferior temporal gyrus
		53	-24	28	5	3,2	R	supramarginal gyrus
Kuhtz-Buschbeck, J.	2009 MNI	0	-3	57	7,7	5,7	L	supplementary motor area
		3	-12	63	7,4	5,6	R	supplementary motor area
		36	57	15	7	5,4	R	middle frontal gyrus
		36	51	24	6,6	5,2	R	middle frontal gyrus
		57	9	9	6,4	5,1	R	opercullum
		48	-57	51	6,3	5	R	inferior parietal lobe
		6	0	72	6,2	5	R	supplementary motor area
		63	-51	33	6,2	5	R	angular gyrus
		3	24	48	6,1	4,9	R	superior frontal gyrus

S4 Table. Peak coordinates of clusters with task specific activity (pelvic floor muscle contraction), not shown in supplement 4. (continued)

		x	y	z	T	Z	Hemisphere	brain area
Nour, S.	2000 Talairach	-24	-66	-48		5,1	L	cerebellum
		2	-56	-24		5,6	R	cerebellum
		2	-44	-8		5,2	R	cerebellum
		-6	-10	-4		4,8	L	anterior mesencephalon
		16	-4	0		5,4	R	globus pallidus
		-16	-8	2		4,7	L	globus pallidus
		28	24	4		4,7	R	insula
		36	-14	8		4,8	R	insula
		-22	-8	72		5	L	superior frontal gyrus
		-6	-18	74		5,1	L	supplementary motor area
		-10	-40	76		5,1	L	post and precentral gyrus
		20	-44	74		5,5	R	postcentral gyrus
		56	-30	24		5,1	R	supramarginal gyrus
Blok. B.	1998 Talairach	-8	10	-8		2,6	L	hypothalamus
Blok. B.	1997 Talairach	50	-2	-12		3,1	R	medial temporal gyrus
		-4	-4	-4		3,4	L	hypothalamus



S1 Figure. Overlap of tasks. Green: Micturition. Red: Pelvic floor muscle contraction.



CHAPTER 3

Whole brain 7T-fMRI during pelvic floor muscle contraction in male subjects

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ABSTRACT

Aims: The primary aim of this study is to demonstrate that 7T-fMRI can visualize the neural representations of the male pelvic floor in the whole brain of a single subject.

Methods: 17 healthy male volunteers (age 20-47) were scanned in a 7T-MRI scanner (Philips Achieva). The scanning protocol consisted of 2 functional runs using a multiband echo planar imaging sequence and a T1-weighted scan. The subjects executed 2 motor tasks, one involving consecutive pelvic floor muscle contractions (PFMC) and a control task with tongue movements.

Results: In single subjects, results of both tasks were visualized in the cortex, putamen, thalamus and the cerebellum. Activation was seen during PFMC in the superomedial and inferolateral primary motor cortex (M1), supplementary motor area (SMA), insula, mid cingulate gyrus (MCG), putamen, thalamus and in the anterior and posterior lobes of the cerebellum. During tongue movement, activation was seen in the inferolateral M1, SMA, MCG, putamen, thalamus and anterior and posterior lobes of the cerebellum. Tongue activation was found in the proximity of, but not overlapping with, the PFMC activation. Connectivity analysis demonstrated differences in neural networks involved in PFMC and tongue movement.

Conclusions: This study demonstrated that 7T-fMRI can be used to visualize brain areas involved in pelvic floor control in the whole brain of single subjects and defined the specific brain areas involved in PFMC. Distinct differences between brain mechanisms controlling the pelvic floor and tongue movements were demonstrated using connectivity analysis.

Keywords: Brain mapping, fMRI, 7 tesla, high-field imaging, single subject, primary motor cortex, pelvic floor.

INTRODUCTION

Pelvic floor disorders (PFDs), such as urinary and fecal incontinence as well as pelvic organ prolapse, are highly prevalent in both men and women.[1] Given the increase of PFD symptoms with increasing age and the steady increase in life expectancy, PFD currently forms a major healthcare problem with significant economic and social burden.[1,2]

The pelvic floor musculature and pelvic organs are innervated by the pudendal and pelvic nerves, the activity of which is controlled by various parts of the central nervous system. Indeed, over the past decades different studies using a variety of imaging techniques have revealed that many different brain areas are involved in voluntary pelvic floor muscle contraction (PFMC).[3-8] In healthy volunteers, group analyses showed that the primary motor cortex, supplementary motor area (SMA), insula, thalamus and cerebellum can all be activated during PFMC.[3,4,8,9] Voluntary control of the pelvic floor must be distinguished from involuntary control of the pelvic floor during continence, which is controlled by separate central pathways.[3]

Interestingly, patients suffering from PFD may show different activations of the central nervous system during PFMC compared to healthy volunteers.[10,11]

FMRI studies using 1.5-or 3-Tesla (T) magnets typically study BOLD (Blood-oxygen-level dependent) responses in groups of subjects, which requires additional smoothing to compensate for the variability of anatomical structures. Obtaining reliable single-subject responses requires higher SNR (Signal-to-Noise Ratio) and BOLD sensitivity. Therefore, the use of dynamic brain imaging as a diagnostic tool in individual PFD patients had so far only limited value in daily clinical practice.

Recently, high resolution (voxel size ~1mm^3) fMRI at increased field strengths (7T) has led to significant improvement in the achievable spatial resolution.[12] The increases in both SNR and BOLD signal at high-fields[12] make single subject imaging possible.[13] Furthermore, 7T-fMRI has been used successfully to map digit representations in individuals.[14] With state-of-the-art 7T-fMRI one can obtain a higher resolution BOLD signals from cortical to cerebellar regions simultaneously.[15]

The primary aim of this study is to demonstrate that 7T-fMRI can visualize the neural representations of the male pelvic floor in the whole brain of a single subject. Secondary aims are to define the involved brain areas in male pelvic floor control and to compare the individual results with our group results in the context of the available literature. Furthermore, we aimed to study the differences of functional connectivity of the involved brain areas between both tasks. Movements of tongue muscles, were chosen as a control task, because this midline motor task is mainly involved in different, well automated voluntary behaviours such as eating and speaking.

MATERIALS AND METHODS

Subjects Approval for this study was given by the Medical Ethics Committee of the Erasmus Medical Center Rotterdam (METC 2015-451). All included subjects provided written informed consent. Seventeen healthy right-handed male volunteers (mean age 29.6 SD ±7.8 years) participated in this study. We limited our study to a single sex, since the male and female pelvic floor motor control should be anatomically distinguished and differences in the central control have not been fully identified.[16] Furthermore, our study is the first to use 7T-fMRI to study pelvic floor representations in single subjects. Given the exploratory design a homogeneous study population was desired. Subject exclusion criteria were any known impairment of urogenital or tongue motor innervation; current or known neurological, psychiatric or urological disorder(s) and contra-indications for MRI.

Stimuli and functional paradigm All subjects completed the same scanning protocol, consisting of two functional runs followed by a T_1-weighted anatomical scan. Functional runs consisted of two motor tasks (pelvic floor contraction and tongue movement), performed using a block paradigm. Prior to the scanning session, all subjects underwent a training session in a mock scanner to ensure correct task execution. During this training session motor tasks were performed as described below. For the task 'pelvic floor muscle contraction', subjects were visually cued to strain their pelvic floor by contracting their anal sphincter or perineum. To prevent patients from contracting the gluteal muscles, they were instructed to lay still on the MRI bed. The motor task 'tongue movement' required subjects to perform horizontal tongue movements. During this condition, subjects were instructed to keep their mouths closed by passively resting the lips and jaws together. Cues were generated in MATLAB using Psychtoolbox (Brainard, 1997) and presented on a 32-inch BOLD screen (Cambridge Research Systems, Rochester, UK). The active condition was indicated by the text 'MOVE' and the rest condition by a fixation cross '+'. The PFMC task consisted of an active condition of 21.5 seconds, in which the subject was instructed to repeatedly contract their pelvic floor followed by 19.5 seconds of rest, this cycle was repeated 12 times with an additional rest condition at the start of the run, resulting in a total scan time of 500 seconds. The tongue movement task consisted of an active condition of 10 seconds followed by a rest condition of 10 seconds. This cycle was repeated 24 times with an additional rest condition at the start of the run, resulting in a total scan time of 490 seconds.

Data acquisition All data were acquired on a 7T-MRI scanner (Philips Achieva) using a volume transmit coil and a 32-channel receive coil (Nova Medical). Functional data was acquired using a multiband echo planar imaging (mb-EPI) sequence with multiband

factor 2.[17] Whole-brain coverage, with the exception of the most inferior regions of the cerebellum and the caudal brainstem, was achieved using the following parameters: voxel size: 1.77x1.77x1.75mm^3, matrix size: 104x127; FOV=184x223mm; number of slices: 70,TR/TE=2000/25ms; flip angle=70°; in-plane SENSE factor R=3. Whole-brain anatomical data was acquired using the MPRAGE sequence with the following parameters: voxel size 0.7x0.7x0.7mm^3, matrix size: 352x353, FOV=246mm; number of slices: 249; TR/TE = 4.4/1.97s, SENSE factors R=1.6 (anterior-posterior) and R=1.5 (right-left); total acquisition time 8'35". To account for the signal loss in infratentorial areas, a dielectric pad of calcium titanate ($CaTiO_3$) was placed just below the inion at the back of the subjects' heads.[18]

Data pre-processing All data was reconstructed on an offline workstation using dedicated reconstruction software (Recon Frame, Gyrotools, Zürich, Switzerland). Further data processing was done in SPM12 (Wellcome Trust Center for Neuroimaging, London, UK). Pre-processing steps included joint image realignment of the functional runs, co-registration of the anatomical image to the resulting mean functional image and smoothing of functional data with a Gaussian kernel (FWHM 2.5mm).

Data analysis For the extraction of the peak activation coordinates, anatomical and functional data was normalized to the standard brain template of the Montreal Neurological Institute (MNI152).

First-level statistical analysis was conducted using the General Linear Model (GLM). Each functional task was modelled as a boxcar convolved with a canonical hemodynamic response function (HRF) and its temporal derivative as basic functions. Realignment parameters were added as nuisance regressors to account for confounding motion effects. In single subjects, activation maps were thresholded at $p<0.05$ voxel-based family-wise error (FWE), if clusters were not found, thresholds were changed to $p<0.001$ (only in putamen and thalamus results). Second-level statistical analysis was conducted using a one-sample t-test on individuals' task responses. Activation maps were thresholded at $p<0.001$ uncorrected for multiple comparisons, if the cluster was not found, the threshold was changed to $p<0.005$ uncorrected. Both single subject and group level cortical activation maps were projected on inflated cortical surfaces created in Freesurfer and sampled halfway the grey matter (projfrac=0.5). In order to aid the inflation process, all images were first bias corrected (bias FWHM=18, sampling distance=2) and resliced to 1mm isotropic in SPM.

Functional connectivity analysis Connectivity analysis was performed by calculating the correlation between time series from different regions of interest (ROIs) in each single subject. ROIs were isolated using individuals' contrast images. Where necessary, for example between primary motor and sensory regions, merged ROIs were manually separated in ITK-SNAP. Subsequently, voxel time series were extracted from each ROI

per single subject and denoised for signal arising from white matter, grey matter and cerebrospinal fluid using linear regression. Furthermore, the task model was added as a regressor of no interest. Connectivity was defined as the linear correlation between time series of different ROIs, which was computed with the Pearson's correlation coefficient. Single subject correlation matrices were used to compute a mean correlation matrix.

To assess the overlap of clusters of both tasks in specific brain areas, the dice index was calculated using the extracted ROI's of the single subjects. The dice index was calculated for overlap in the M1, SMA, insula and cerebellum ROIs.

RESULTS

The scanning protocol was completed in all 17 subjects. Data concerning 4 subjects was excluded due to motion artefacts (>1mm displacement), yielding a total of 13 subjects for in-depth analyses.

Single subject and group analyses following pelvic floor muscle contraction

PFMC resulted in significant activation of various different brain regions following analyses of both single subjects and groups (for group results: Table 1). The superomedial primary motor cortex (M1) was activated in all subjects. In the group analysis this cluster was split into two separate clusters, one more anterior and the other more posterior on M1 (Fig. 1). Moreover, on M1, a second, more inferolateral cluster was found bilaterally in 11/13 subjects. This inferolateral M1 cluster was also activated bilaterally in the group analysis (Fig. 1). In 11 subjects' active clusters were found in the putamen (8 bilateral/3 unilateral). Thalamus activation was found in 10 subjects (5 bilateral/5 unilateral). In group analysis this resulted in combined activation of the putamen and the thalamus in both hemispheres (Fig. 2). Concerning the cerebellum, activation in lobule IV was seen bilaterally in 7 subjects and unilaterally in 1 subject (indicated by circles, Fig. 3). More posterior, in lobule VI, an active cluster was found bilaterally in 6 subjects and unilateral in 5 subjects (Fig. 3). In the posterior lobe of the cerebellum, specifically in lobule VIII, active clusters were found during PFMC in 2 subjects bilaterally and in 6 subjects unilaterally (data not shown). In the group analysis, cerebellar activation was found in lobule IV bilaterally, comparable to the single subject results. The cluster seen in single subjects in lobule VI was found unilateral in the left hemisphere of the cerebellum in the group analysis. Group analysis did not show activation in lobule VIII.

Connectivity analyses following pelvic floor muscle contraction

Connectivity analysis was performed in the nine individuals who showed active voxels in all ROIs except for the thalamus, the activity of which was not present in a sufficient

Table 1. Results of group activation whole-brain (MNI) with height threshold T=3.93 p<0.001 uncorrected, * T=3.05 p<0.005 uncorrected.

		Pelvic				Tongue			
Region	***hemisphere***	***x***	***y***	***z***	***peak T***	***x***	***y***	***z***	***peak T***
SupMed M1	L	-12	-26	66	8.77	-	-	-	-
	R	12	-24	66	5.79	-	-	-	-
InfLat M1	L	-48	-2	52	3.33*	-54	-8	40	8.31
	R	42	-2	54	3.72*	62	4	28	7.62
SMA	L	-2	-16	68	6.56	-2	-2	60	4.03
	R	2	-6	64	7.62	6	0	64	5.12
MCG	L	-4	-6	46	5.61	-2	2	38	3.20*
	R	8	-4	46	4.83	10	14	40	3.60*
insula	L	-32	0	12	6.28	-34	-10	14	3.63*
	R	46	4	2	6.10	38	-2	12	6.01
putamen	L	-26	-8	12	12.98	-28	-4	-6	3.85*
	R	28	-4	14	9.93	28	2	-6	5.39
thalamus	L	-12	-16	6	5.11	-14	-20	0	5.86
	R	10	-16	8	4.13	12	-16	0	7.28
cerebellum	L	-16	-48	-14	5.29	-20	-60	-24	8.28
	R	10	-46	-10	3.91*	20	-64	-20	7.06

Abbreviations: SupMed: superomedial, M1: Primary motor cortex, InfLat: inferolateral, SMA: Supplementary motor area, MCG: Mid cingulate gyrus.

number of subjects to include it as an ROI in this analysis. Figure 4 shows the results of the connectivity analysis.

Superomedial M1 was highly correlated with the SMA and less correlated with the other ROIs. SMA was correlated with superomedial M1, but also other cortical ROIs like the MCG, the insula and the inferolateral M1 during PFMC.

Activation during tongue movements

Tongue movements resulted in large active clusters lateral of M1 in all subjects (Fig 1). The SMA was found active in all but 3 subjects. Tongue movements showed in 4 subjects' bilateral activation in the putamen and in 1 subject unilateral. In 6 subjects bilateral thalamus activation was found, and in 4 subjects unilaterally (Fig 2).

Cerebellar activation during tongue movement in single subjects was found consistently in lobule VI bilaterally. In 8 subjects' bilateral activation was also found in lobule VIII in the posterior cerebellum and in 2 subjects unilaterally (Fig 3). Group analysis showed activity in M1, the SMA, the anterior insula, MCG, putamen, thalamus (presumably in the VL/VA nuclei) and the cerebellum (Table 1). The connectivity analysis (n=13) showed that M1 correlates with SMA, the insula and the cerebellum (Fig. 5).

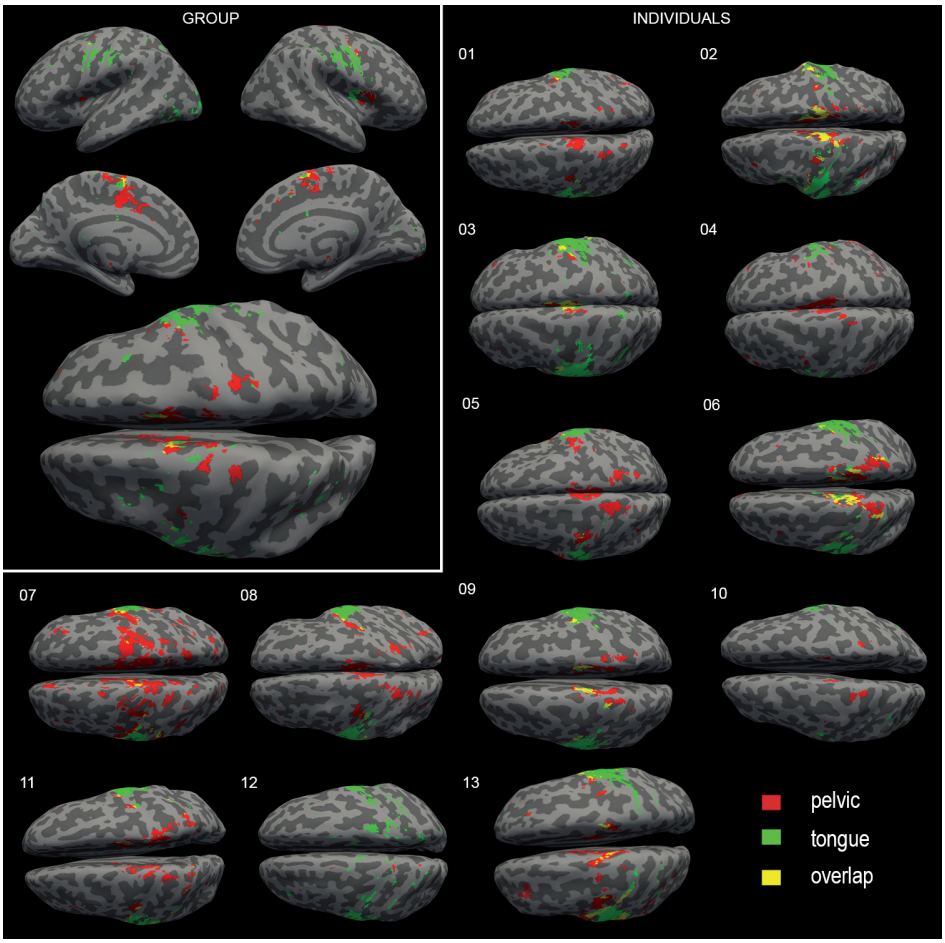

Figure 1. Results of both PFMC and tongue movement tasks presented on the cortex. Left upper corner: Inflated MNI brain representing group analysis ($p<0.005$ uncorrected). The rest: brain-inflations of single subjects representing single subject activation ($p<0.05$ FEW).

Overlap

The overlap of activation clusters of PFMC and tongue movement in M1, SMA, insula and cerebellum was calculated using the ROIs of the same subjects as used for the functional connectivity. In the M1 ROIs there was no overlap, the dice index was 0.0 ± 0.0 (mean ± standard error (SE)). For SMA (0.12 ± 0.05), insula (0.09 ± 0.04) and especially the cerebellum ROIs (0.04 ± 0.02), the overlap was minor.

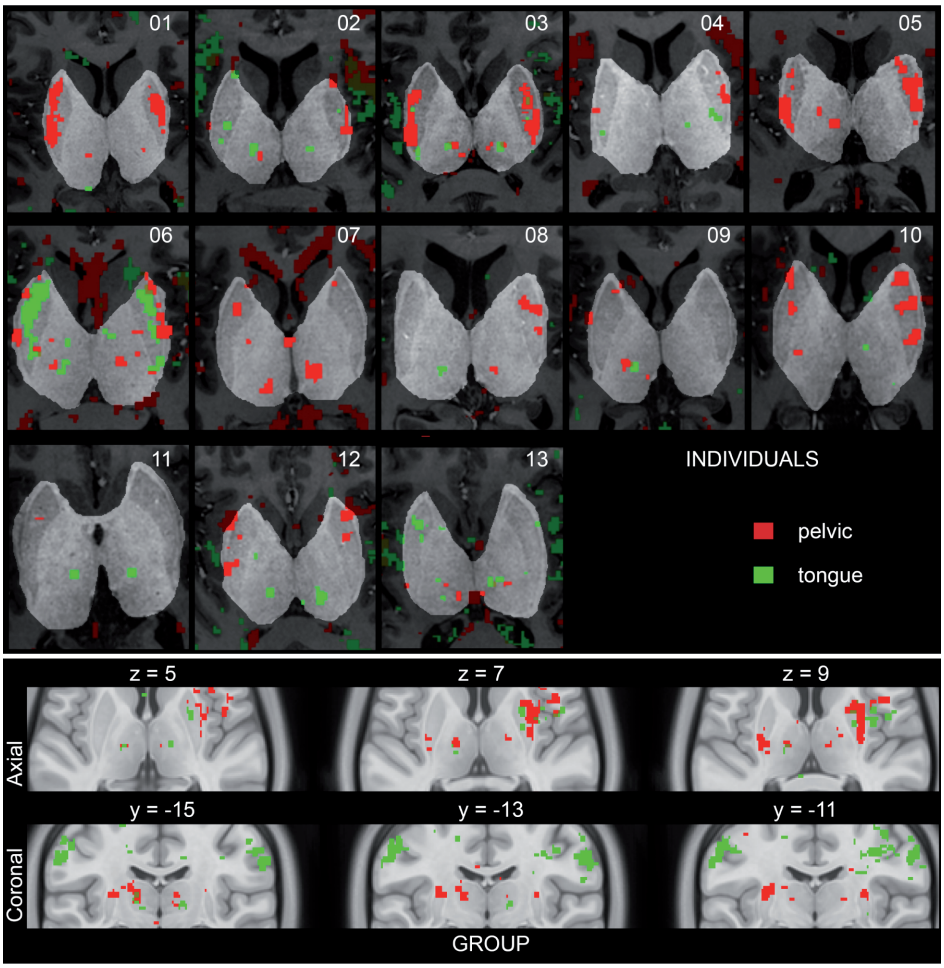

Figure 2. Activation in the putamen and thalamus in single subjects (p<0.001 uncorrected) and group analysis (p<0.001 uncorrected).

DISCUSSION

This is the first study demonstrating that 7T-fMRI is a suitable technique to study motor behaviour of the pelvic floor in the whole brain of male individuals, showing concomitant cortical, subcortical and cerebellar activation. The superomedial M1, inferolateral M1, SMA, MCG, the putamen, the thalamus (VL/VA) and the cerebellum were activated during contraction of the pelvic floor. The similarities and differences between the results of the individuals and the group results, tell us more about the genesis of group results and applicability of group results in individuals.

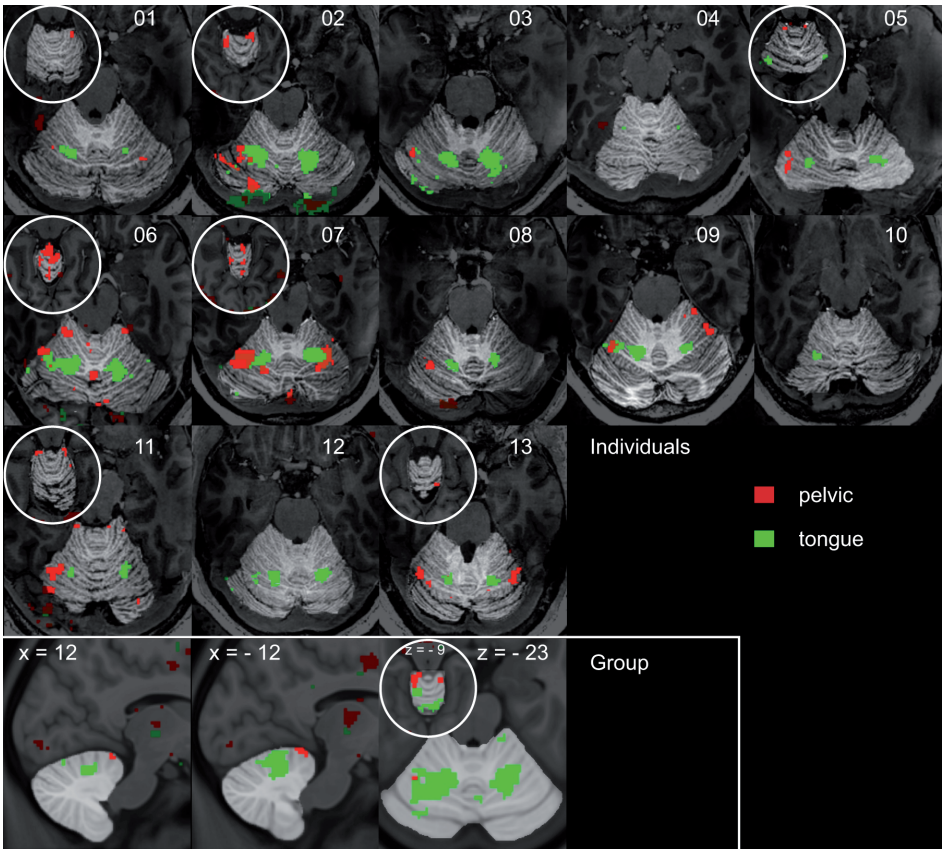

Figure 3. Axial and sagittal coupes of the group analyses of the cerebellum and axial coupes of cerebellar activation in single subjects with in circles a more superior coupe of the cerebellum. Single subjects threshold T=5.2, p<0.05 FEW, group threshold T=3.05, p<0.005 uncorrected.

Cortical representations

Our results showed a strong activation bilaterally in superomedial M1 during contraction of the pelvic floor consistently in all individuals and in groups analyses. Activation of M1 during PFMC was first demonstrated using PET,[3] which supplemented the earlier described concept of the homunculus of Penfield and Rasmussen.[19] The activation found in M1 during PFMC, in the "hip-region" of the homunculus, is in line with other conducted neuroimaging studies using group analysis.[3,6,7,9,20] In addition, during PFMC, in both single subject- and group analysis, a bilateral inferolateral M1 cluster was found, directly superior of the tongue clusters. Two studies found activation in the precentral gyrus, 3 cm from the midline and suggested that this activation was associated with concomitant contraction of the abdominal muscles.[3,22] In other publications, a similar cluster is visible in some figures, but has not been described in detail.[10,21,23] The current 7T-fMRI results further pinpoint the exact areas in the human motor cortex involved in

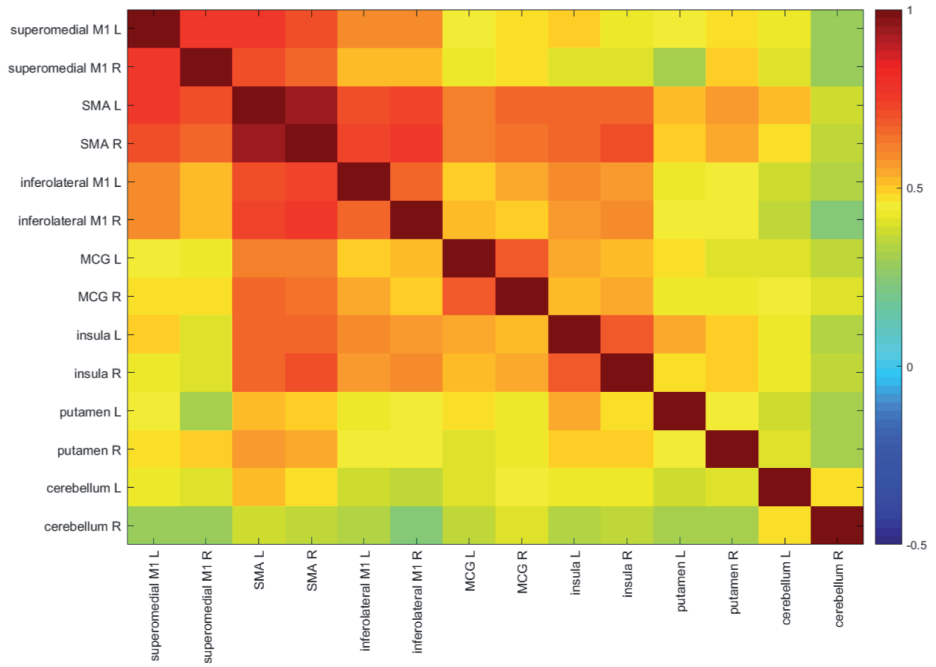

Figure 4. Mean correlation of regions of interest during pelvic floor muscle contraction in n=9.

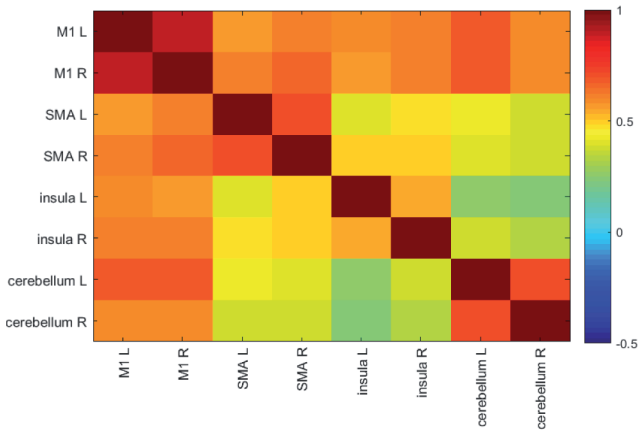

Figure 5. Mean correlation of regions of interest during tongue movement n=13.

PFMC. The group results showed moderate overlap of PFMC and tongue clusters in the SMA, but no overlap in M1. The strong somatotopy of M1 has been described extensively, and overlap of clusters in M1 was therefore not expected. Research investigated

a possible somatotopy of the SMA and suggested that the cranial to caudal body is represented from anterior to posterior respectively in the SMA.[24,25] Our results did not clearly demonstrate this somatotopy. In these smaller cortical body representations, the shorter distances between neighboring body parts results in lager overlap in the BOLD results. Note that this does not necessarily mean that the neural circuits for pelvic and tongue are shared in SMA, just that they are spatially closer.

The connectivity analysis showed a strong correlation between the superomedial M1 and the SMA during PFMC. Previously, it has been suggested that the SMA has a facilitatory effect on M1 during voluntary motor tasks.[4,26] Di Gangi Herms et al., compared cortical activation of women with stress urinary incontinence before and after pelvic floor muscle therapy (PFMT) using 3T-fMRI.[23] Prior to the start of the PFMT significant clusters were found in the SMA during PFMC; after 12 weeks of daily PFMT this cluster in the SMA was not found during PFMC and activation in the M1 was smaller and more focused. Our subjects had practiced voluntary PFMC just prior to the 7T-fMRI, and in the connectivity analysis we see that the SMA was strongly connected to the M1 and other cortical and subcortical areas. The connectivity of the SMA to other brain areas during the tongue task was less pronounced than during PFMC and active clusters shown in the SMA during tongue movements were smaller (Fig 1). Voluntary tongue movement is necessary for speaking and chewing, usually a highly conditioned tasks. This indicates that the SMA is especially important in less conditioned movement control, such as PFMC. In this context, it is important to realize that cortical and subcortical activations was much more consistent among the participants during tongue movement, than during PFMC (Fig 1).

Putamen

In the present study, PFMC and tongue movement resulted in all single subjects and in the group analysis, in activation of the putamen, especially in the caudal putamen (fig 2). Although specific caudal activation of the putamen during PFMC and tongue movement has not been described previously, activation in the putamen as a whole has been observed before during both tasks.[6-8,27] The putamen is part of the cortico-basal ganglia (BG)-thalamocortical-loop which participates in motor action selection.[28]

Thalamus

The last part of the cortico-BG-thalamocortical-loop is the VL/VA nuclei of the thalamus, which, in turn, project to the motor cortex.[29,30] Our results showed bilateral activation in the thalamus during both tasks. In individuals and groups analyses, activation was seen possibly in the VL/VA nuclei (fig 2). Activation was not found in all single subjects, but when found, it was consistently found on the same location. The current study is the first to show these results consistently in individuals. Previous studies on PFMC and tongue movement showed activation in thalamus without specification of a thalamic subnucleus.[5,6,27]

The cingulate gyrus

The mid cingulate gyrus was activated bilaterally during PFMC and tongue movements. The location is comparable to previous studies during similar tasks: repetitive PFMC with empty bladder.[4,5,23] The involvement of this cluster can be explained by the presumed role of the MCG in the decision to perform a reward based motor task.[31]

The insula

Bilateral anterior insular activity was found during both tasks. Insular activity during PFMC and tongue movement is described before, but not particularly in the anterior insula.[4,20,23,32] The conducted connectivity analysis showed that the insula is connected to cortical structures like the SMA but also to the MCG. Evidence suggests that the anterior insula is in particular strongly connected to the MCG to regulate attention related responses, for instance pelvic floor contractions for retaining continence.[33] Additionally, the insula shows an increased connectivity to the motor cortex in patients with chronic pelvic pain syndrome compared to healthy controls, explained by the insular involvement of visceral sensations.[10] In future this might be of great interest to further explore the pathophysiology of PDF's.

Cerebellum

The cerebellum contains a double homunculus, one in the anterior lobe and a reversed in the posterior lobe.[34] We investigated anterior cerebellum activation not only for groups but also for single subjects. We found clusters in lobules I-IV of the cerebellum during PFMC, and clusters in lobule VI during tongue movement. This 'up-side-down' somatotopic representation of the human body agrees with previously obtained somatotopic maps.[35] This is the first study to show these results during PFMC in single subjects, which are comparable to two other studies on group analysis of cerebellar activations during PFMC.[3,6] In single subjects, tongue movement created large and consistent clusters in the cerebellum compared to PFMC. The ratio of the size of these tongue and PFMC clusters appear comparable to the ratio of the found clusters on the primary motor cortex.

Tongue movements as control task

Tongue movements were chosen as a control task, since this midline motor task can be controlled both voluntarily and involuntarily, like PFMC. PFMC presumably diverges from tongue movement, because it may involve more affective-emotional aspects. Moreover, tongue movement is a more conditioned motor task, which explains the different connectivity during the two tasks. Existing literature describes active clusters during tongue movement in the same brain areas as the active clusters found in the present study with comparable coordinates,[27,36] also for the cerebellar clusters.[35]

Technical insights

This study analysed both single subject results and group data. In the group results, during PFMC, activation in superiomedial M1 is split into two separate clusters with less activation compared to the single subject results. The smoothing is indispensable when performing group analysis in view of the large inter-subject variability of the brain anatomy. Consequently, this might cause disappearance of the less significant findings in individuals, like the present clusters in M1. The high folding of the superior end of M1 further complicates group analysis done in a 3D space. The increased BOLD signal at 7T-fMRI makes high resolution single subject activation maps available, and allows for a more accurate understanding of the central organization in humans.[12] Cortical single subject results during PFMC have been visualized previously at 3T (see figure 3 in Yani et al.[21]). The direct comparison between 3T and 7T results within individuals is left for future work.

Conclusion

We have demonstrated that 7T-fMRI can visualize the neural representations in the whole brain involved in voluntary control of the pelvic floor in healthy male subjects. This has been done for the first time with whole brain coverage and high-field imaging, creating a high spatial resolution and a more accurate understanding of the involved brain areas. Our study shows that voluntary PFMC is represented in M1, SMA, MCG, insula, putamen, thalamus and the cerebellum. Our connectivity analysis showed distinct differences between brain mechanisms controlling PFMC and tongue movement. The present high field fMRI study may help to design future 7T studies in individual patients. These studies should provide new insides on the pathological circuits in order to improve clinical practice.

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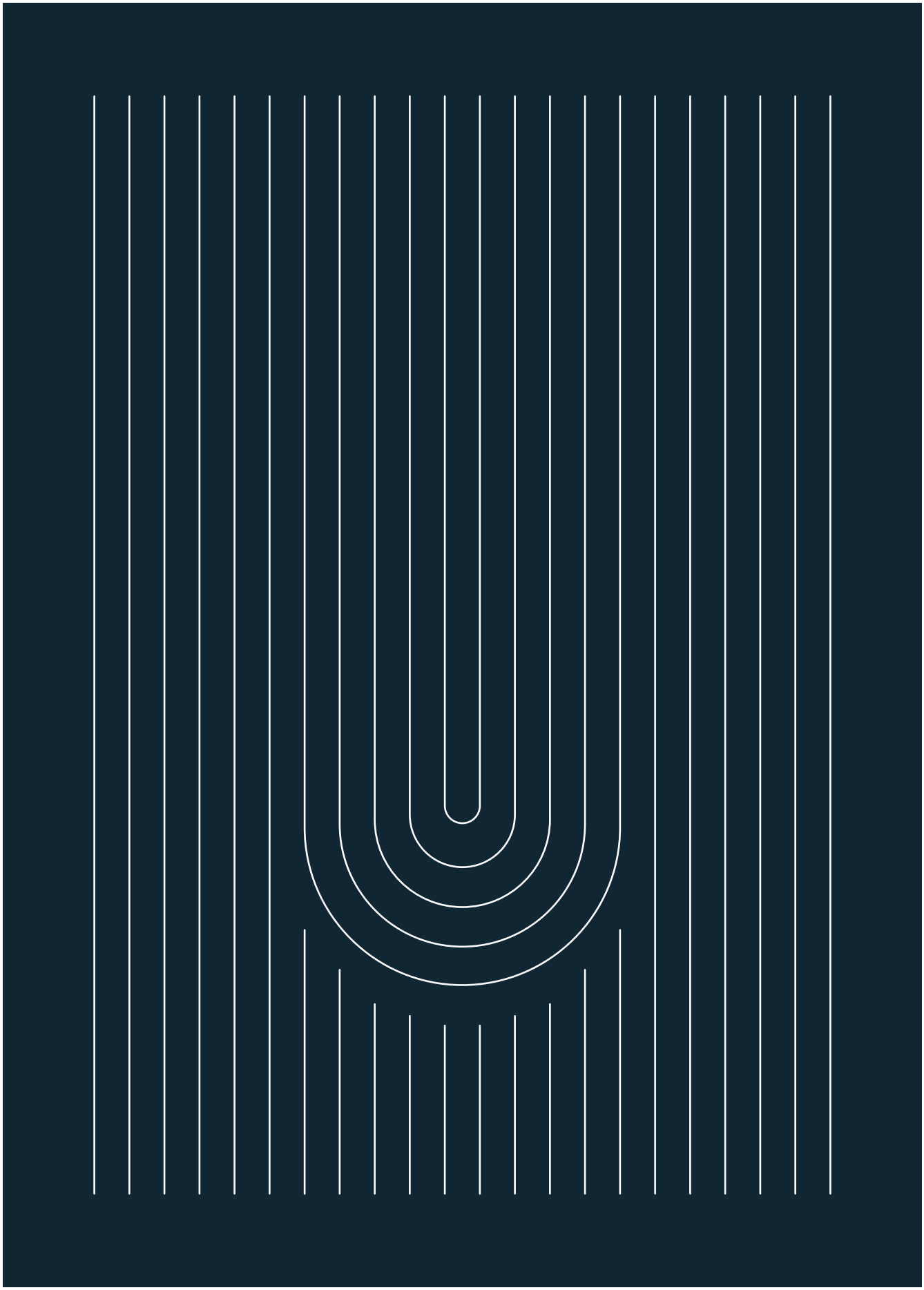
Ethical approval: The local ethics committee approved this study (MEC-2015-451)

Informed consent: All volunteers participating in this study gave written consent.



CHAPTER 4

Single subject and group whole-brain fMRI mapping of male genital sensation at 7 Tesla

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ABSTRACT

Processing of genital sensations in the central nervous system of humans is still poorly understood. Current knowledge is mainly based on neuroimaging studies using electroencephalography (EEG), magneto-encephalography (MEG), and 1.5- or 3- Tesla (T) functional magnetic resonance imaging (fMRI), all of which suffer from limited spatial resolution and sensitivity, thereby relying on group analyses to reveal significant data. Here, we studied the impact of passive, yet non-arousing, tactile stimulation of the penile shaft using ultra-high field 7T fMRI. With this approach, penile stimulation evoked significant activations in distinct areas of the primary and secondary somatosensory cortices (S1 & S2), premotor cortex, insula, midcingulate gyrus, prefrontal cortex, thalamus and cerebellum, both at single subject and group level. Passive tactile stimulation of the feet, studied for control, also evoked significant activation in S1, S2, insula, thalamus and cerebellum, but predominantly, yet not exclusively, in areas that could be segregated from those associated with penile stimulation. Evaluation of the whole-brain activation patterns and connectivity analyses indicate that genital sensations following passive stimulation are, unlike those following feet stimulation, processed in both sensorimotor and affective regions.

INTRODUCTION

Human sexual behaviour is characterized by inter- and intrapersonal intimacy. This includes tactile stimulation of the external genitalia, giving rise to both discriminative and affective sensations.[1] Despite the evident role of the brain in the perception of touch, it remains unclear how tactile input from the external genitalia is centrally processed in the healthy individual.

The primary and secondary somatosensory cortices (S1 and S2) are well-recognized as the main cortical areas involved in processing the discriminative properties of tactile input. Over the years, studies investigating genital touch in women and men have generally focused on S1 due to the counterintuitive location of the genitalia beneath the feet in the sensory homunculus.[2,3] Some confirm this location, recording cortical evoked responses deep in the medial wall of S1 during electrical stimulation of the dorsal nerve of the penis (DNP; principal sensory nerve of the penis).[4-6] Later functional magnetic resonance imaging studies (fMRI) studies, however, demonstrated significant brain activation dorsolateral in the groin region of S1 in response to passive tactile stimulation of the external genitalia.[7,8] Findings regarding the involvement of S2 in processing tactile penile input show more consistency, demonstrating bilateral activation during both electrical[6] and tactile stimulation.[7,8] Other brain regions have also been associated with processing the affective properties of touch. This includes not only the insula,[9] but also the anterior cingulate (ACC) and medial prefrontal cortex (mPFC) during tactile stimulation of the forearm.[10] Bilateral activation of the insula has been demonstrated in response to both electrical[6] and tactile penile stimulation.[8] Activation of the midcingulate cortex (MCC), but not ACC, and mPFC have only been reported following tactile stimulation of the male genitalia.[8]

Recently, high field (7 Tesla) fMRI has emerged as a superior neuroimaging technique to study human brain function *in vivo*. Increases in signal-to-noise ratio (SNR) and blood-oxygenation-level dependent (BOLD) sensitivity at 7T[11,12] have made it possible to acquire data with high spatial acuity and demonstrate robust activation in individuals. Recent studies showcasing these advantages include mapping the representation of individual digits[13] and the lower limb[14] in S1 at the single subject level. Given the substantial intersubject variability of neural representations as well as the need to treat patients as individuals, it has become eminently important to study human brain function at the level of individuals.[13-15] Moreover, signal advantages gained at 7T can not only be observed at a limited field of view such as in S1, but also in more extended whole-brain acquisitions[16] including the cerebellum.[17]

In the present study, we used 7T fMRI to acquire high-resolution neural representations of male genital sensation in the whole-brain at both single subject and group level. In order to do so, subjects underwent passive tactile stimulation of the genitalia in a way that minimized sexual arousal. Passive tactile stimulation of the medial aspect of the feet, performed in an equivalent manner as genital stimulation, served as a control task. The feet were deliber-

ately chosen not only because of their location adjacent to the genitalia in the homunculus, but also as a more emotionally neutral stimulus. In addition, the medial aspect of the feet is involved in successful electrical therapies for an overactive bladder, like posterior tibial nerve stimulation[18] or transcutaneous electrical nerve stimulation.[19] Therefore, current findings regarding supraspinal activation during tactile stimulation of the feet could provide more insight into which regions are targeted and affected by this treatment modality.

We hypothesized that the representation of the external genitalia is located in the groin region of S1, lateral to the feet. Furthermore, we hypothesized that passive tactile stimulation of the genitalia would lead to activation of brain regions associated with processing of both sensorimotor discriminatory (S1 & S2) and affective (insula, MCC and mPFC) properties of touch at both single subject and group level. In contrast, passive tactile stimulation of the feet would lead to activation of brain regions predominately associated with processing discriminatory properties of touch.

RESULTS

Four subjects were excluded from further analysis due to excessive spike head motion. The remaining thirteen subjects were included in first and second level of analyses. None of the subjects had an erection whilst undergoing tactile stimulation by the experimenter. Tactile stimulation of the penile shaft evoked significant activation superomedial and inferolateral in S1, S2, ventral premotor cortex (vPMC), posterior and anterior insula, posterior midcingulate gyrus (pMCG), mPFC, thalamus and cerebellum. Responses observed for left and right brushing were similar, and therefore added into a single contrast. Tactile stimulation of the feet evoked significant activation superomedial and inferolateral in S1, S2, vPMC, posterior insula, thalamus and the cerebellum.

Representations in S1

Tactile stimulation of the penile shaft and the feet evoked significant activation ($p < 0.05$ family wise error (FWE)) during whole-brain analysis in 11 out of 13 subjects (Fig. 1). Bilateral activation was observed superomedial and inferolateral in response to stimulation of the penile shaft. Unilateral activation was observed superomedial in the right hemisphere in response to stimulation of the left foot. Bilateral activation was observed superomedial in response to stimulation of the right foot. In addition, we also observed unilateral activation inferolateral in the left hemisphere. In single subjects, feet activation clusters extended anteromedial in S1 along the postcentral gyrus. Summation of these elongated clusters resulted in fractioning of feet activation clusters at group level (Fig. 2). Slight overlap was seen between penile shaft and feet activation clusters. Nevertheless, shaft clusters were consistently found lateral to the feet in the left and right hemispheres, both at single subject and group level.

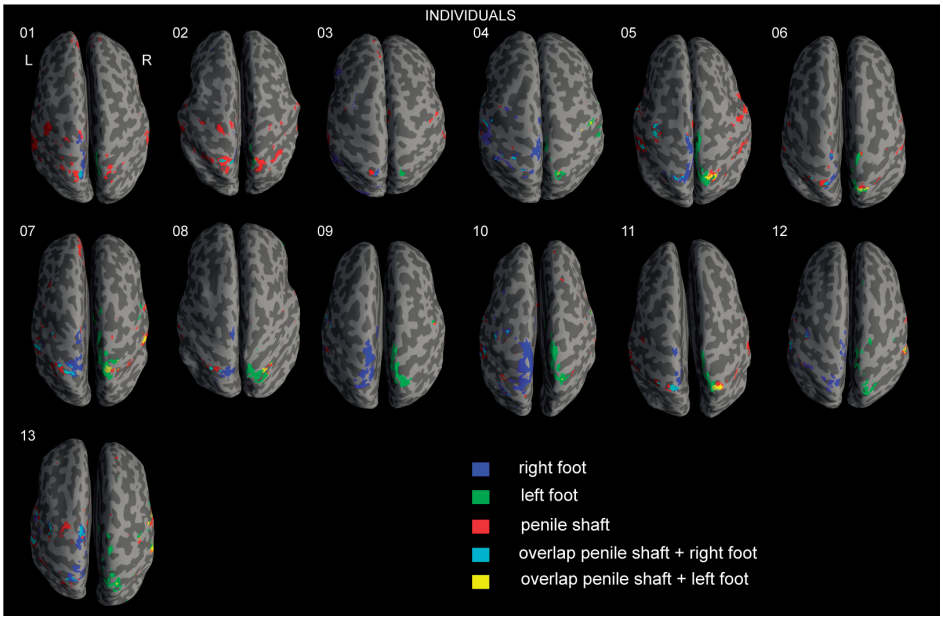

Figure 1. Single subject cortical activation patterns. Single subject activation maps ($p < 0.05$ FWE) from all individuals (n=13) displayed on inflated anatomical images showing top-view. Legend in bottom-right corner indicating task specific color codes.

Whole-brain results

To further determine which cortical areas are implicated in processing tactile input from the genitalia and the feet outside of S1, we also examined whole-brain responses (Table 1). Tactile stimulation of the penile shaft elicited bilateral activations in S2, posterior and anterior insula, vPMC and the cerebellum. In single subjects, unilateral and bilateral activations were seen in the pMCG, mPFC and thalamus. At group level, unilateral activation in the pMCG was seen in the left hemisphere and bilateral activation was seen in the mPFC. We also observed subcortical activation in the medial and posterior regions of the thalamus, correlating with reported locations of the medial dorsal (MD) and ventral posterolateral (VPL) nuclei.[20,21] Tactile stimulation of the left foot elicited bilateral activations in S2, unilateral activation in the posterior insula in the right hemisphere, and unilateral activation in the cerebellum in the left hemisphere. Subcortical activation was observed posterior in the thalamus in the right hemisphere, presumably the VPL. Tactile stimulation of the right foot elicited bilateral activations in S2, posterior insula, and unilateral activation in the vPMC in the left hemisphere. Subcortical activation was observed posterior in the thalamus (VPL) in both hemispheres.

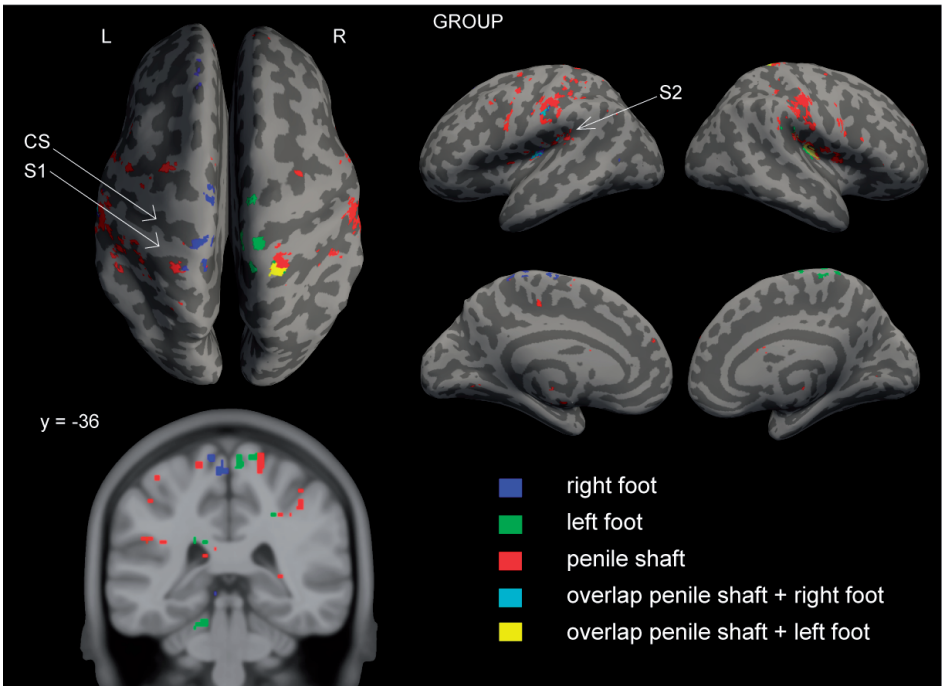

Figure 2. Group cortical activation patterns. Group activation maps ($p < 0.005$ uncorrected for multiple comparisons; n=13) displayed on an inflated MNI template showing lateral, medial and top view. A coronal section from the MNI template (y=-36) is shown in the bottom-left corner, where the penile shaft is clearly located lateral to the feet in S1. Legend in the bottom-right corner indicating task specific color codes.

Representation in the cerebellum

At lower statistical thresholds, we observed significant activation in the anterior (lobules I-IV) and superior posterior lobe (lobule VI) of the cerebellum at both single subject ($p < 0.001$ uncorrected for multiple comparisons) and group level ($p < 0.005$ uncorrected for multiple comparisons) (Fig. 3). Shaft and feet representations were found in symmetrical locations in both cerebellar hemispheres across 8 out of 13 single subjects (Fig. 3). Tactile stimulation of the penile shaft evoked significant bilateral activation in lobule VI in the posterior lobe, part of the cerebrocerebellum. In 2 out of 13 individuals (#11, #13) activation was also seen just posterior to feet clusters in lobule IV. Tactile stimulation of the feet evoked significant unilateral activation in lobules IV in the anterior lobe, part of the spinocerebellum. In 4 out of 13 individuals (#04, 07, 12, 13) activation was also seen more posterior adjacent to the shaft clusters in lobule VI. At group level this was seen for the right foot in the contralateral cerebellar hemisphere (Fig. 3).

Table 1. Whole-brain group activation in response to stimulation of the penile shaft and feet versus rest

		Penile shaft				Foot (left)				Foot (right)			
Region	**Hemisphere**	**x**	**y**	**z**	**t-value**	**x**	**y**	**z**	**t-value**	**x**	**y**	**z**	**t-value**
superomedial S1	L	-18	-38	68	3.39					-4	-38	72	7.90
	R	18	-40	68	3.77	6	-36	70	6.36	18	-40	68	6.07
S2	L	-42	-30	-22	4.13	-48	-36	26	4.36	-44	-30	20	5.39
	R	40	-30	24	6.19	46	-30	24	5.17	42	-30	22	5.26
inferolateral S1	L	-58	-16	34	6.57					-62	-16	36	5.63
	R	56	-18	32	4.38								
vPMC	L	-58	6	32	3.42								
	R	56	6	28	3.66								
posterior insula	L	-36	-16	16	3.13					-36	-18	16	6.74
	R	40	-12	14	4.33	34	-14	16	9.04	36	-16	16	5.93
anterior insula	L	-36	0	12	2.66								
	R	36	2	14	3.05								
pMCG	L	-12	-24	42	2.12								
	R												
mPFC	L	-4	52	26	1.89								
	R	12	60	28	1.81								
thalamus	L	-12	-6	8	2.25					-22	-24	12	5.30
	R	18	-22	4	1.68	22	-22	12	4.70	16	-22	12	3.71
cerebellum	L	-26	-54	-26	2.35	-14	-36	-22	5.09				
	R	20	-62	-24	2.73					20	-34	-26	4.11

Table 1. Brain regions, MNI coordinates and peak t-values are listed. All activation for the penile shaft is reported using a global null conjunction analysis ($p < 0.005$ uncorrected for multiple comparisons, t-value > 1.52). All activation for the left and right feet are reported using a one sample t-test ($p < 0.005$ uncorrected for multiple comparisons, t-value > 3.05). S1: primary somatosensory cortex; S2: secondary somatosensory cortex; vPMC: ventral premotor cortex; pMCG: posterior midcingulate gyrus; mPFC: medial prefrontal cortex.

Functional Connectivity

We also assessed the functional connectivity between timeseries of regions of interest (ROIs) for both functional tasks separately (Fig. 4 and Fig. 5). For the penile shaft, timeseries from the superomedial and inferolateral S1, S2, vPMC, posterior insula and the right anterior insula showed moderate correlation (range ρ 0.44 - 0.60). The left anterior insula showed weak correlation (range ρ 0.36 - 0.49) with the superomedial and inferolateral S1, S2, vPMC and posterior insula. Timeseries from the pMCG and cerebellum showed weak correlations overall with other ROIs.

For the left foot, timeseries from superomedial S1 in the right hemisphere showed a strong correlation with the S2 and posterior insula ROIs on the same side, whereas correlation with S2 in the left hemisphere was weaker (Fig. 5A). Timeseries from the

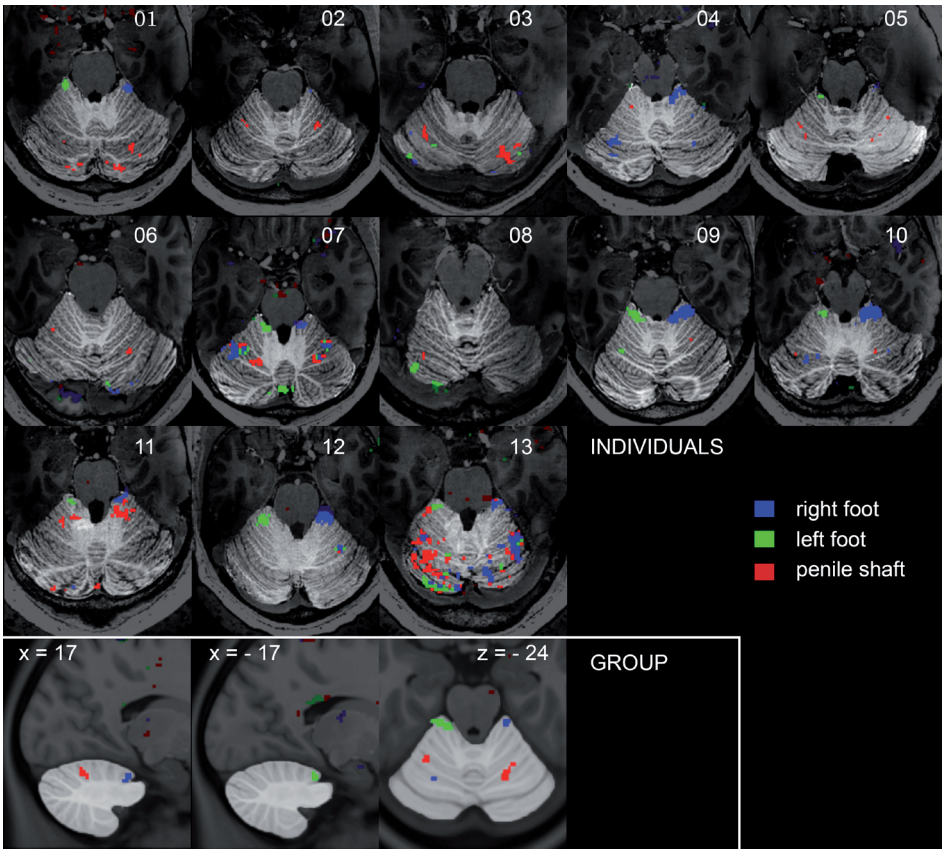

Figure 3. Single subject and group cerebellar activation patterns. Single subject activation maps from all individuals ($p < 0.001$ uncorrected for multiple comparisons) displayed on axial sections containing maximum number of representations. Group activation maps ($p < 0.005$ uncorrected for multiple comparisons, n=13) displayed on sagittal and axial sections from the MNI template (x and z-coordinates in top-left corner indicate position in MNI space). Legend in bottom-right corner indicating task specific color codes.

cerebellum showed weak correlations overall with other ROIs. A similar, yet inverted, correlation pattern was observed for the right foot. Timeseries from superomedial S1 in left hemisphere showed high correlation with the S2 and posterior insula on the same side, whereas correlation with S2 in the right hemisphere was weaker (Fig. 5B). Timeseries from the cerebellum showed weak correlations overall with other ROIs.

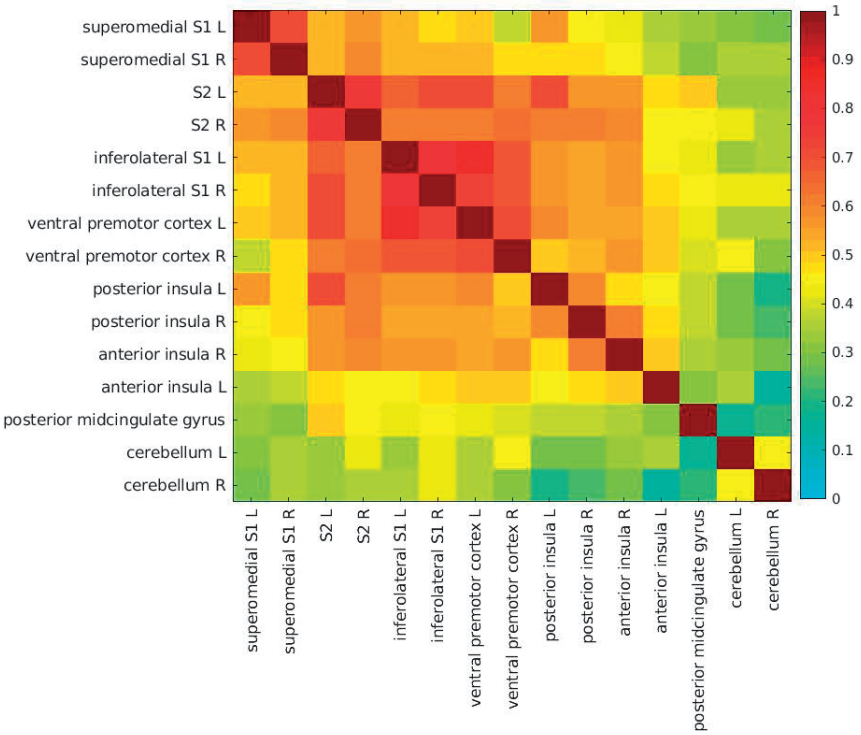

Figure 4. Mean connectivity matrix for penile shaft activation displaying connectivity between regions of interest. Individual connectivity matrices of 9 single subjects were first generated using a Pearson's correlation coefficient, and subsequently used to generate a mean connectivity matrix. Regions of interest included are labeled along axes.

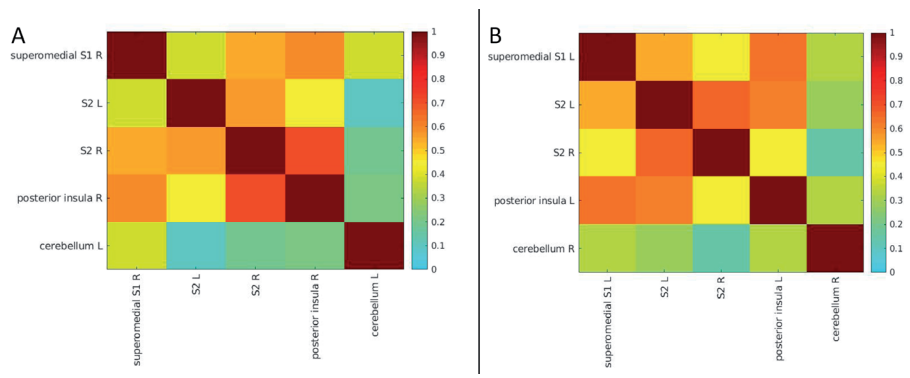

Figure 5. Mean connectivity matrix for left (A) and right (B) foot activation displaying connectivity between regions of interest. Individual connectivity matrices of 10 single subjects were first generated using a Pearson's correlation coefficient, and used to generate a mean connectivity matrix. Regions included are labeled along the axes.

Distances

The distances between activation foci of penile shaft and feet representations in S1 and the cerebellum were measured (Table 2). In S1, vertex distances were measured over the cortical surfaces created during the inflation process in Freesurfer. This gives a more true representation of distances between cortical representations due to the high degree of folding of the postcentral gyrus. Since the cerebellum is not included in the inflation process, Euclidean distances were measured between cerebellar activation foci of penile shaft and feet representations. The distance between neighbouring body representations reflects the amount of cortical space taken up by those representations.[22] For example, a piano player will have larger digit representations than average, leading to a measurably larger distance between the thumb and the little finger. If, for example through underuse, the penile shaft representation gets smaller, this should have an effect on the distance between penile shaft and foot activation foci.

Table 2. Distances between group penile shaft and foot activation foci in S1 and cerebellum

	Hemisphere	Distance (mm)
penile shaft - foot (S1)	L	27.5
	R	26.8
penile shaft - penile shaft (superomedial- inferolateral S1)	L	64.8
	R	63.1
penile shaft - foot (Cb)	L	20.9*
	R	28.1*

Table 2. The distances between penile shaft and foot activation foci in both hemispheres at group level. Brain regions in which distances were measured are indicated in brackets. Distances measured in Euclidean space are indicated with an asterisk. S1: primary somatosensory cortex, Cb: cerebellum

DISCUSSION

The present study is the first to investigate genital touch with the extensive field of view as supported by 7T imaging, and by doing so it provides novel data on the precise representations of the genitalia in the human brain, in particular those of hindbrain areas like the cerebellum that were often omitted with other approaches. By exploiting the increased BOLD sensitivity and specificity available at 7T, we obtained data with high spatial acuity and anatomical specificity. These clearly demonstrate that the genitalia are located in the groin region and not below the feet in S1. Furthermore, considerable differences were observed in whole-brain activation patterns in response to tactile stimulation of the genitalia as opposed to the feet. Tactile stimulation of the penile shaft evoked significant activations of discriminative (sensorimotor) and affective (emotional) brain regions, whereas tactile stimulation of the feet evoked significant activations of

mainly discriminative brain regions. In addition, functional connectivity was assessed between activation clusters for both the genitalia and feet. This is the first study to report on functional connectivity of genital sensation.

Some have described the representation of the genitalia to be positioned in the medial wall below the representation of the feet in S1,[4-6] while others describe a more dorsolateral representation between the trunk and leg.[7,8] At both single subject and group level, our data clearly indicates that the genitalia are represented dorsolateral of the feet in S1 (Fig. 1 and Fig. 2), similar to what has been reported by previous studies using 3T fMRI.[7,8] Animal studies investigating genital representations have also described this location measuring extracellular recordings in primates[23] and more recently using cortical microstimulation in rats.[24] Despite applying unilateral stimulation to the penile shaft, we observed bilateral activation in S1 irrespective of stimulation side. This corresponds well with findings showing that cutaneous regions situated in the midline of the body are represented bilaterally in S1.[25] Interestingly, studies using electrical stimulation of the DNP to locate the genitalia in S1 repeatedly demonstrated activation deep in the interhemispheric fissure. Cortical evoked responses elicited by electrical stimulation of the DNP were consistently located beneath those elicited by stimulation of the posterior tibial nerve.[4-6] It should be noted, however, that earlier techniques (e.g. EEG/MEG) used to measure brain responses offered poor spatial resolution. In addition, it is known that differences in evoked brain potentials can be observed when comparing electrical to tactile stimuli, further questioning this method when investigating the processing of physiological somatosensory stimuli.[26] In the present study, passive tactile stimulation of the medial aspect of the feet served as a control, analogous to electrical stimulation of the posterior tibial nerve. We expected to see activation in S1 lateralize in the contralateral hemisphere, as can be seen during stimulation of the left foot (Table 1). During stimulation of the right foot, however, significant yet weaker activation was also observed in the ipsilateral hemisphere (Table 1). Absence of lateralization in S1 has also been demonstrated during tactile stimulation of only the right and not the left hand in right-handed subjects.[27] The authors suggested this asymmetry is associated with hand preference and proficiency. Humans not only have a preference for left- or right-handedness, but also left- or right-footedness which can be seen in for instance football players.[28] In the present study we did not assess footedness prior to inclusion, however, we suggest ipsilateral activation in S1 during stimulation of the right foot may be the result of right-footedness.

Activation in S1 evoked during tactile stimulation of the feet extended anteromedial along the postcentral gyrus. Beneath this activation cluster, in most single subjects and at group level, activation was also observed deep in the interhemispheric fissure in response to tactile stimulation of the genitalia (Fig. 2; medial-view left hemisphere). At

a closer examination, this area corresponds to the pMCG and not S1, which had been suggested previously.[4]

Although it was not the objective of this study, these data also allow a comparison of habituation effects during the functional tasks. Inspection of mean signal intensity curves superomedial in S1 show comparable habituation between shaft and feet stimulation (Fig. 6), indicating that task saliency was comparable.

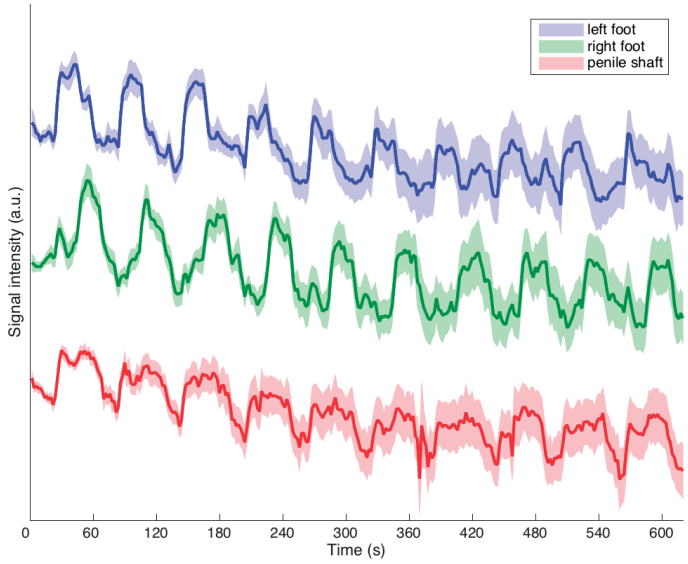

Figure 6. Mean signal intensity (in arbitrary units, a.u.) over time (in seconds, s) superomedial in S1 during tactile stimulation of the penile shaft and feet. The stimulation paradigm included 10 blocks (stimulation versus rest) each lasting 60 seconds with an additional rest block at the start resulting in a total scan duration of 620 seconds per task. For viewing purposes, curves were centered around separate baseline values. All timeseries were normalized prior to averaging across subjects. The shaded error bars indicate the standard error over subjects.

Penile shaft and feet representations showed several areas of overlap (Fig. 1). Correspondingly, in women, overlap has been demonstrated between the genitalia and nipple.[29] This may have impeded earlier intraoperative mapping experiments by Penfield and colleagues, and it may partly clarify why genital sensations were so hard to induce.[2] Furthermore, this finding may also help to provide insight into why electrical therapies such as dorsal genital nerve[30] and posterior tibial nerve[18,19] stimulation share a similar inhibitory effect on bladder activity.

Inferolateral in S1, we observed robust bilateral activation during tactile stimulation of the penile shaft and, to a lesser extent, in the left hemisphere during tactile stimulation of the right foot. Activation inferolateral in S1 has also been described during electri-

cal stimulation of the clitoris[31] and mechanical stimulation of the rectum suggesting this area may be involved in processing pelvic sensory information.[32] Furthermore, it has been argued that this cluster is in close proximity to the representation of the face in S1 and represents stimulus related activation rather than face/mouth movements due to discomfort.[31] We agree with this observation for the following reasoning. First, robust bilateral activation inferolateral in S1 was consistently seen in single subjects and the group. Prior to sensory tasks, subjects were instructed to lie still, breathe as they normally would and not make any movements. The current stimulus (brushing with a toothbrush) was well tolerated by participants and none reported discomfort after the scanning procedure. Hence, it is unlikely subjects consequently made similar mouth/face movements due to discomfort while they were explicitly instructed not to do so. Second, inferolateral activation clusters in S1 showed high functional connectivity to the superomedial S1 clusters and also other associative sensorimotor areas such as S2, the insula and vPMC (Fig. 4). This suggests that activation in this region is related to tactile genital stimulation and not due to co-occurring mouth/face movements.

Bilateral activation of the vPMC was observed during tactile stimulation of the penile shaft and unilateral activation of the vPMC was observed in the left hemisphere during tactile stimulation of the right foot. In both primates and humans, this area has been described to be sensitive to multisensory input, including tactile stimuli.[33,34] Accordingly, previous studies have demonstrated similar activation of this area during both tactile[8] and electrical[31] stimulation of the genitalia.

Activation of the posterior insula was observed during tactile stimulation of the penile shaft and the feet, whereas activation of the anterior insula was only observed during genital stimulation. Posterior insula activation has been described earlier and is associated with gentle touch processing.[9,35] Stimulation paradigms used in these studies included gentle stroking with a brush, similar to the stroking paradigm with a toothbrush in the present study. On the other hand, activation of the anterior insula was observed during stimulation of the penile shaft and not the feet. Other cortical areas solely activated during stimulation of the penile shaft include the pMCG and mPFC. These areas have been associated with the processing of affective/emotional properties of touch[10,36], which fits well with the specific character of sensations (i.e. sexual or erotic) that may arise during tactile stimulation of the genitalia as opposed to the feet. In the current study, however, we did not assess potential sexual or erotic sensations experienced during stimulation making direct correlations not possible. Future research including psychometric measurements (e.g. by means of questionnaires) with both arousing and non-arousing stimuli is needed to determine whether activation of affective/emotional brain regions correlates with the perception of such sensations.

For the penile shaft, activation was observed posterior in the thalamus in the right hemisphere, corresponding to the VPL. In the left hemisphere activation as observed

more anteriorly, corresponding to the MD (Table 1). Sensations of touch are processed through the dorsal column-medial lemniscus pathway projecting to the thalamus, in particular the VPL, and from thereon to the somatosensory cortex.[20] Our findings suggest the MD nucleus is also involved in processing genital touch. Accordingly, activation was also observed in the mPFC, where MD afferents project to.[20] In addition, electrophysiological studies in cats and rats have identified multiple bilateral subregions of the thalamus receiving inputs from the genital tract, including the VPL and MD.[24,37] Here, unilateral activation of the VPL in the left hemisphere and MD in the right hemisphere may, however, be the result of the small cluster size and weak BOLD signals measured in the thalamus using the current whole-brain acquisition protocol (Table 1). On the other hand, for the left foot, contralateral VPL activation was observed and for the right foot bilateral VPL activation was observed. Accordingly, contralateral S1 activation was observed for the left foot and bilateral S1 activation for the right foot.

Here we also mapped the representation of the penile shaft and feet in the anterior and posterior lobes of the cerebellum (Fig. 3). In line with previous findings, tactile stimulation of the feet evoked ipsilateral activation in lobule IV.[38,39] In some single subjects, activation was also observed more posterior in the cerebellum in both ipsilateral and contralateral hemispheres. At the group level, sparse activation was observed only in the contralateral hemisphere. We expected the genitalia would be represented just posterior to the feet in lobule IV, supporting previous fMRI studies in humans describing a somatotopical layout of the body in the anterior lobe of the cerebellum orientated anterior-posteriorly.[38-40] Surprisingly, in most single subjects and at the group level, genital representations were found more posterior in lobule VI in both cerebellar hemispheres (Fig. 3), seemingly posterior to the cerebellar hand representations.[40] In 2 individuals (#11, #13), activation was also observed adjacent to the feet representations in lobule VI, where we would have expected the genitalia to be represented. In these subjects, though, we also observed activation more posterior in lobule VI. When comparing cerebellar representations to those found in S1, the feet representations found anterior in lobule IV appear to be part of the somatomotor network[41] also including the superomedial S1 feet and shaft representations. In contrast, the shaft representations found posteriorly in lobule VI may be part of a more associative frontoparietal network[41] also incorporating the inferolateral S1 cluster.

In the present study, timeseries from cerebellar clusters showed low functional connectivity to any of the other ROIs. Regions that showed the highest degree of connectivity were the inferolateral S1 and vPMC in the right hemisphere. When inspecting the topographic organization of cerebrocerebellar circuits based on intrinsic functional connectivity, lobule VI is largely mapped to the inferolateral S1 and vPMC.[41] Our data suggest that these cerebellar representations of the genitalia in lobule VI belong to this particular cerebrocerebellar network. The relatively low functional connectivity

demonstrated here may be the result of methodological differences such as task-based functional connectivity vs resting-state connectivity and sample sizes N=9 vs N=1000.

Functional connectivity was assessed for both functional tasks, no previous studies have reported on this. For the penile shaft, this was mainly done to see if we could demonstrate separate cerebral networks involved in processing genital touch (i.e. discriminative vs affective). Brain regions such as superomedial and inferolateral S1, S2, vPMC, the posterior insula and right anterior insula showed high functional connectivity to each other. On the other hand, the pMCG, left anterior insula and cerebellum showed low overall connectivity to other brain regions. Interestingly, for the feet, superomedial S1 representations showed high connectivity with S2 and the posterior insula on the ipsilateral side, whereas connectivity with S2 on the contralateral side was low. This suggests that, although bilateral activation of S2 was observed, there is some lateralization and dominance of the contralateral S2. Moreover, we observed high functional connectivity between the posterior insula and S2 in the same hemisphere, which is in accordance with the finding that these cortical areas are reciprocally connected.[42]

We acknowledge, however, that the task-based functional connectivity analysis in our study does not give a measure of intrinsic connectivity of neural networks in contrast to resting-state fMRI. In addition, measures of functional connectivity demonstrated here are related to our stimulation paradigm (i.e. brushing with a toothbrush). Other studies using different stimulation paradigms to investigate genital touch may produce different connectivity patterns.

The use of ultra-high field (7T) fMRI here provided considerable benefits compared to neuroimaging techniques used in previous studies investigating genital touch such as EEG, MEG and 3T fMRI.[4-8] Due to significant gains in SNR at 7T, we were able to acquire data with much higher spatial resolution (1.77 x 1.77 x 1.75 mm^3), unmatched by previous studies. Furthermore, while no direct comparisons were made, it is plausible 7T fMRI offers increased BOLD sensitivity and allows detection of smaller effects facilitating increases in statistical strength when conducting both single subject and group analyses compared to fMRI at lower field strengths (1.5- & 3T).[17,43] On the other hand, the relative contribution of physiological noise also increases at higher field strengths. 7T fMRI for instance, is more susceptible to false positive activation caused by subject head motion, potentially leading to higher exclusion rates in comparison to fMRI at lower field strengths. By employing a multiband EPI-sequence, whole-brain coverage including the cerebellum was achieved whilst preserving high spatiotemporal resolution. The current study is the first investigating genital sensation with such an extensive field-of-view and thereby the first to report on cerebellar representations of male genital sensation. This achievement may partly result from the fact that we placed a dielectric pad containing $CaTiO_3$ posterior of subjects' heads, which has been shown to increase both cerebellar T1-weighted anatomical coverage and detection of T2*-weighted BOLD signals.[44]

Conclusion

In conclusion, using 7T fMRI, we present neural representations of genital sensation with unprecedented spatial resolution and whole-brain coverage in both single subjects and the group. We clearly show the genitalia are represented in the groin region in S1 and not below the feet. Whole-brain responses and additional connectivity analyses revealed that passive penile stimulation evoked significant activation in brain regions that can be segregated from those associated with feet stimulation. Genital sensations are processed in both sensorimotor and affective brain regions, whereas feet sensations are processed in sensorimotor regions. These differences may contribute to the specific character of sensations (i.e. sexual or erotic) that are associated with stimulation of the external genitalia.

MATERIALS AND METHODS

Subjects

This study was conducted in agreement with the principles specified by the Declaration of Helsinki. Approval for the current study was given by the Medical Ethics Committee of the Erasmus Medical Center Rotterdam (METC 2015-451). All subjects provided written informed consent before entering the study. 17 healthy right-handed male subjects (mean age ± SD: 29.6 ± 7.8 years) participated in this study. Subjects were asked to take off their trousers and placed in a supine position on the MRI-bed.

Stimuli and functional paradigm

All subjects completed the same scanning protocol, consisting of functional runs followed by a T1-weighted anatomical scan of the whole-brain for co-registration of functional data. Two sensory tasks were performed using a block paradigm. These tasks included subjects undergoing tactile stimulation of the penile shaft and medial aspect of the left and right foot. During both runs, an experimenter was positioned at the entrance of the scanner bore. Tactile stimulation was delivered using a commercially available toothbrush attached to a stick. The experimenter received audio cues indicating when and where to brush on MR-compatible headphones, generated in MATLAB using the Psychophysics Toolbox Version 3 (http://psychtoolbox.org/). The left and right penile shaft were brushed for a duration of 20 s respectively, followed by 20 s of rest (no brushing). This sequence was repeated 10 times with an additional rest period of 20 s at the start of both runs, resulting in a total scan time of 620 s per run. Brushing was done in a proximal to distal direction at a frequency of approximately 1Hz and performed by the same experimenter for all subjects to minimize inter-subject stimulation variability.[13] For this study, a toothbrush was used to deliver tactile stimulation with the aim to mimic a physiological stimulus without inducing sexual arousal. The brushing of a toothbrush

is a good alternative for human touch[7,45] and can comfortably be executed while standing at the entrance of the scanner bore. Subjects were given a towel which they were instructed to place on the abdomen. Subsequently, subjects were instructed to place the penis on the towel in order to prevent skin-to-skin contact with the thigh and abdomen during the tactile stimulation. Prior to the actual scanning session, all subjects underwent a training session in a mock scanner. This gave subjects the opportunity to get acquainted with the tactile stimulus (brushing of a toothbrush). During this training session, tactile stimulation was delivered in a similar manner as described above.

Data acquisition

All functional and structural data were acquired on a 7T MRI scanner (Philips Achieva) using a volume transmit coil and a 32-channel receive coil (Nova Medical). Functional data was acquired using a multiband echo planar imaging (mb-EPI) sequence with multiband factor 2. Whole-brain coverage, including the anterior lobe of the cerebellum, was achieved using the following parameters: voxel size 1.77 x 1.77 x 1.75 mm^3; matrix size: 104 x 127; FOV = 184x223 mm^2; number of slices: 70; TR/TE = 2000/25 ms; flip angle = 70°; in-plane SENSE factor R = 3. Whole-brain anatomical data was acquired using the MPRAGE sequence with the following parameters: voxel size 0.7 x 0.7 x 0.7 mm^3, matrix size: 352 x 353, FOV = 246 mm; number of slices: 249; TR/TE = 4.4/1.97 s, SENSE factors R = 1.6 (anterior-posterior) and R = 1.5 (right-left); total acquisition time 8'35". In addition, to account for signal loss in infratentorial areas, a dielectric pad containing calcium titanate ($CaTiO_3$)[46] was placed posterior of the subjects' heads.[46]

Image preprocessing

All data was reconstructed on an offline workstation using dedicated reconstruction software (ReconFrame, Gyrotools, Zürich, Switzerland). Further data processing was done in SPM12 (Wellcome Trust Center for Neuroimaging, London, UK). Pre-processing steps included joint image realignment of all four functional runs, co-registration of the anatomical image to the resulting mean functional image and smoothing of functional data with a Gaussian kernel (FWHM 2.5 mm). For the extraction of peak activation coordinates, functional data was normalized to the standardized brain template of the Montreal Neurological Institute (MNI). Additionally, inflated cortical surfaces were created in Freesurfer (http://surfer.nmr.harvard.edu/) using single subject anatomical images and the MNI template. In order to aid the inflation process, all images were first bias corrected (bias FWHM = 18, sampling distance = 2) and resliced to 1mm isotropic in SPM.

Whole-brain analyses

First level statistical analysis was conducted using the General Linear Model (GLM). Each functional task was modeled as a boxcar convolved with a canonical hemodynamic re-

sponse function (HRF) and temporal derivative as basis functions. Realignment parameters were added as nuisance regressors to account for confounding motion effects. The response for each task was estimated independently from the others. Activation maps for tactile stimulation of the left and right penile shaft showed a high degree of overlap in both hemispheres, and were therefore conjoined into a single contrast using a global null conjunction analysis[47] thresholded at $p < 0.05$ voxel-based FWE). Activation maps for tactile stimulation of the left and right foot were generated as separate contrasts and thresholded at $p < 0.05$ FWE.

Second level statistical analysis was conducted using a one-sample t-test on individuals' task responses. Likewise, at group level, left and right shaft contrasts were conjoined using a global null conjunction analysis $p < 0.005$ uncorrected for multiple comparisons. Activation maps for tactile stimulation of the left and right foot were again thresholded at $p < 0.005$ uncorrected for multiple comparisons. Both single subject and group level cortical activation maps were projected on inflated cortical surfaces created in Freesurfer and sampled halfway the mid-cortical depth in order to avoid vascular artifacts at the pial surface.

Functional connectivity analyses

To further evaluate activation of different networks (i.e. discriminative vs affective), we computed the correlation between timeseries from different ROIs in single subjects. Timeseries were extracted from individual pre-processed contrast images, which were realigned, co-registered and smoothed as described earlier. For the penile shaft, ROIs included were S1, S2, vPMC, posterior and anterior insula, pMCG and the cerebellum. ROIs were isolated using individuals' contrast images and successfully identified in 9 out of 13 individuals. Activation in the thalamus and mPFC could only be observed in 4 and 5 subjects respectively, and were therefore not included in the functional connectivity analysis. For the feet, included ROIs were the S1, S2, posterior insula and cerebellum. Again, ROIs were isolated using individuals' contrast images and were successfully isolated in 10 out of 13 individuals. Overlapping activation clusters were manually separated in ITK-SNAP (http://www.itksnap.org/). Subsequently, voxel timeseries were extracted from each ROI per single subject and denoised for signal arising from white matter, gray matter and cerebrospinal fluid using linear regression. Connectivity was defined as the linear correlation between timeseries of different ROIs, which was computed with the Pearson's correlation coefficient. Single subject correlation matrices were used to compute a mean correlation matrix for both the penile shaft and feet.

Data availability

The datasets analyzed during the current study are available in NIFTI format for interested researchers. Please contact the corresponding author to make a request.

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AUTHOR CONTRIBUTIONS

SL, JH, WZ and BB contributed to the concept and design of the study. SL and IG conducted the experiments. SL and IG analyzed the data with contribution of WZ. SL, IG, CZ, WZ and BB interpreted the results. All authors contributed to and reviewed the manuscript.

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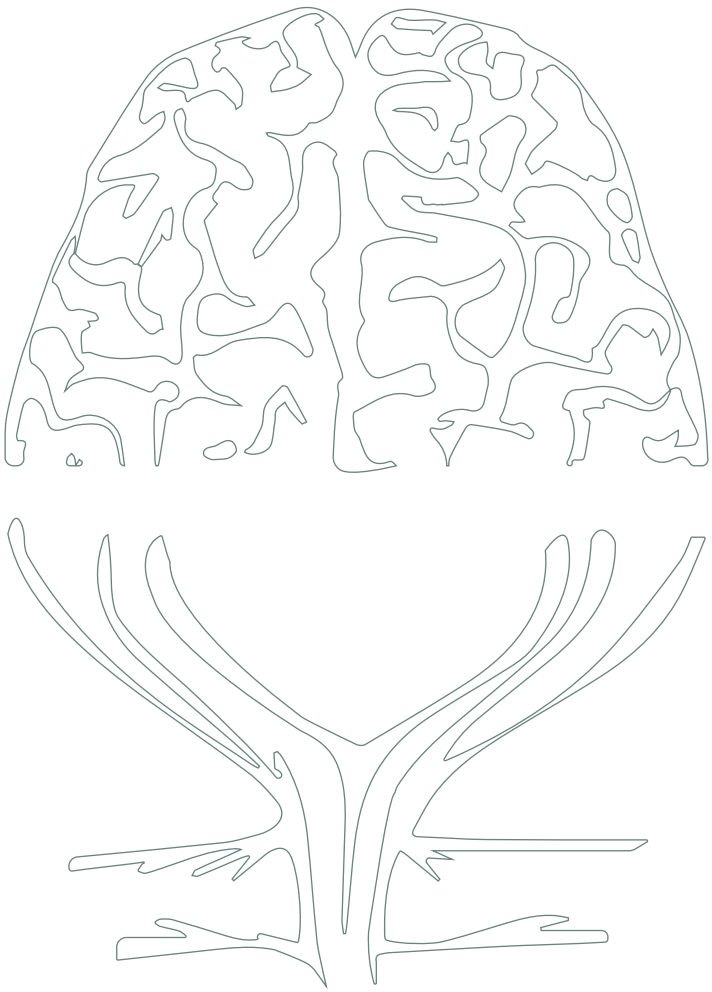
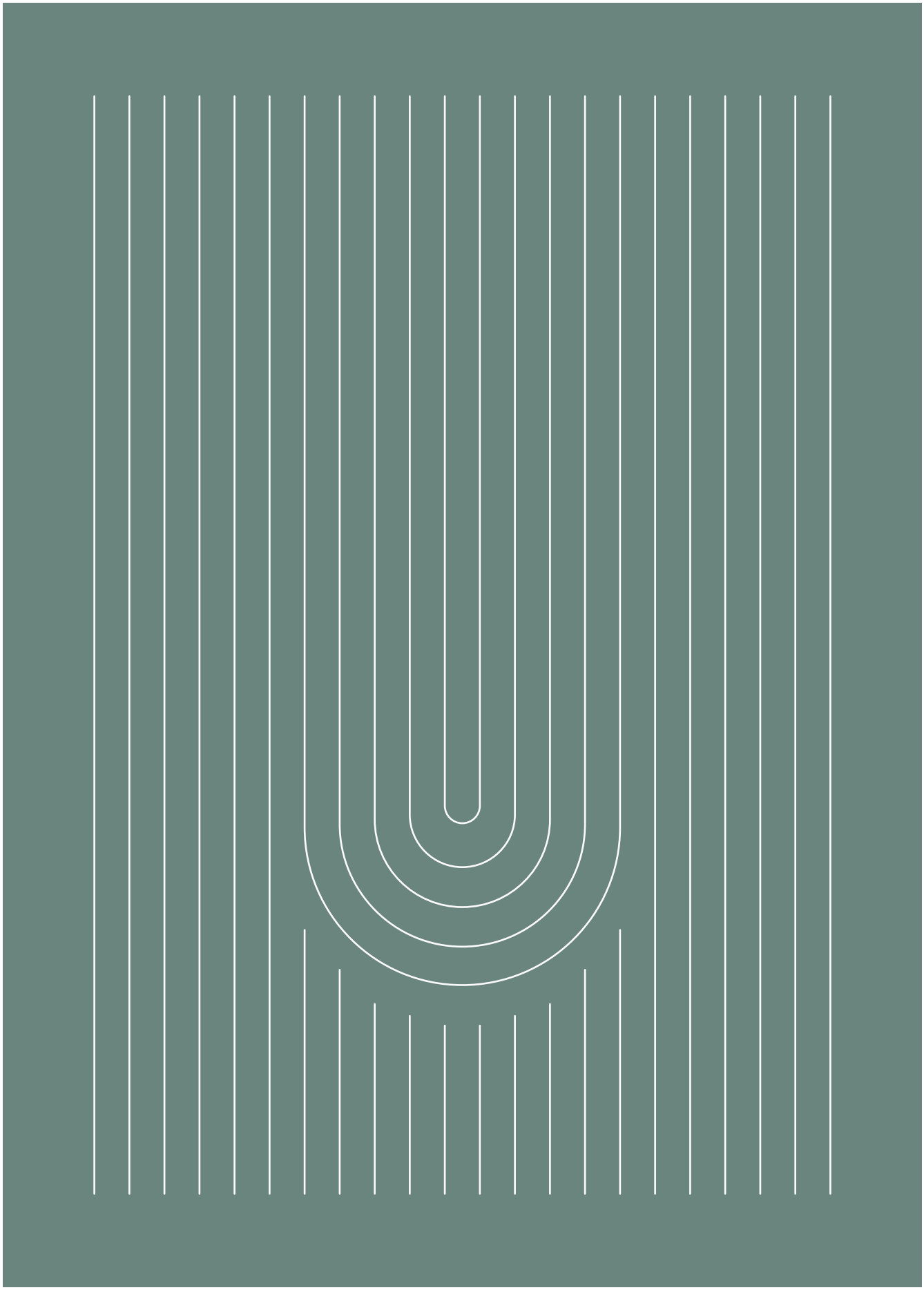


PART II

DIAGNOSTICS AND TREATMENT IN FUNCTIONAL UROLOGY



CHAPTER 5

Acute effect of sacral neuromodulation for treatment of detrusor overactivity on urodynamic parameters

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ABSTRACT

Aim: The aim of this study is to evaluate the acute effects of sacral neuromodulation (SNM) on various urodynamic parameters.

Methods: Patients with overactive bladder (OAB) and detrusor overactivity (DO) who were planned for percutaneous nerve evaluation (PNE) were included. Directly after the PNE a urodynamic study (UDS) was performed. The stimulation was turned off during the first UDS (UDS 1), and during the second filling cycle, stimulation was turned on (UDS 2). The UDS was followed by a test phase of one week and the bladder diaries were evaluated during an outpatient clinic visit. Primary outcome measures were the differences in UDS parameter values with SNM off and on.

Results: Ten female patients were included in the study and completed the study protocol. Eight patients showed ≥50% improvement of symptoms following a test phase. There were no differences between UDS 1 and UDS 2 in the UDS parameters: Bladder volume at first sensation, bladder volume at first DO, highest DO pressure, bladder capacity, maximum flow rate (Qmax) and pressure at maximum flow rate (pQmax).

Discussion: None of the above mentioned urodynamic parameters was influenced by acute sacral neuromodulation in patients who responded to sacral neuromodulation. To the best of our knowledge this is the first study investigating the acute effects of SNM on bladder function.

Keywords: urodynamics, neuromodulation, sacral root, overactive bladder, acute effect

INTRODUCTION

Overactive bladder (OAB) is a condition defined as urgency, with or without urgency urinary incontinence, usually associated with frequency and nocturia.[1] The prevalence is described to be between 11 – 16% worldwide and is expected to increase as a result of the aging of the population causing a high burden on society.[2,3] The pathophysiology of this highly prevalent disease is still being explored and the value of urodynamics (UDS) in OAB is investigated. About 54.2% of patients with symptoms of OAB show detrusor overactivity on UDS.[4]

Currently, first-line treatment consists of conservative treatments like pelvic floor muscle therapy (PFMT) and second-line treatment of oral anticholinergics or betamimetics. Neither of these treatments is very efficient. Research shows that the benefit of PFMT is not maintained on the long term and more than 50% stop anticholinergic drug treatment within the first three months because of lack of benefit and adverse effects.[5]

Sacral neuromodulation (SNM) is a safe and effective third line therapy for symptoms of OAB.[6] SNM is supposed to suppress involuntary bladder contractions and to normalize bladder sensation via afferent nerve modulation.[7] Prior to implantation of a sacral neuromodulator, a percutaneous nerve evaluation (PNE) or first stage tined lead placement test (FSTLP) is done to evaluate the efficacy in the OAB patient. In patients with an improvement of ≥50% of symptoms, evaluated with bladder diaries, a sacral neuromodulator is implanted.[5]

Different properties of SNM in bladder dysfunction have been investigated; such as the onset of action, the wash-out period and the effectiveness of intermittent and on-demand SNM.[8-11] An argument for intermittent or on-demand SNM was a longer battery life, and consequently fewer surgical replacements, although the need for intermittent SNM is less urgent since the introduction of the rechargeable battery.[12] In some studies it was found that efficacy of SNM decreased after 5 years.[13] Adaption by the nervous system was postulated as the cause of this.[10,14] Other studies found that the therapeutic effect of SNM was stable after 5 to 6 years.[6,15]

Implantable ultrasound devices and potentiometers to detect bladder filling and contractions have been studied in pigs.[16,17] Such devices could be helpful in the development of a feedback system in which the neuromodulator automatically activates when the detrusor pressure is increasing.[18] If acute SNM has direct inhibitory effects on bladder function, such a closed-loop feedback system could be of potential value for patients with OAB. Studies in rats demonstrated an acute inhibitory effect of neuromodulation on bladder contractions.[19]

Whether UDS parameters can predict the success of SNM in patients has been investigated, but no predictive UDS parameters have been found.[20,21] Moreover, when comparing UDS parameters before and during SNM (six months stimulation), several UDS

parameters significantly changed; bladder volume at first sensation, bladder capacity, maximum detrusor pressure and Qmax.[22-24] The acute effect of SNM on UDS has never been investigated.

Therefore, the aim of this study is to evaluate the acute effect of SNM on the different UDS parameters.

MATERIALS AND METHODS

The present study was approved by the local medical research ethics committee (METC 2017-471). Prior to the study, written informed consent was obtained from all patients.

Patients

Patients with OAB and urodynamically proven detrusor overactivity, who were scheduled for PNE, were eligible for screening. Exclusion criteria were age under 18 years, intravesical botulinumtoxinA injections in the past 9 months, predominant stress urinary incontinence, bladder pain syndrome, neurogenic bladder, urinary tract infection, having an indwelling catheter, previous radiotherapy of the pelvis, pregnancy and malignancies of the lower urinary tract.

Intervention

Our standard care procedure for PNE was performed and is as follows. All anticholinergics and β3-adrenoceptor-agonists were stopped two weeks prior to the PNE. The PNE is done in the outpatient clinic under local anesthesia. PNE's were performed using the PNE-sets of Medtronic (4 patients) or Axonics (6 patients). A test electrode is inserted into one of the S3 foramens of the sacrum. Placement is considered correct if stimulation is felt in the vagina, penis, perineum or anus. The electrode is then connected to the external nerve stimulator (ENS). In the current study, the patient underwent a urodynamic study (UDS 1) after placing the electrode but before the ENS was turned on. This study was performed according to ICS criteria, using a 7 Fr transurethral double lumen catheter and an 8 Fr rectal pressure sensor.[25,26] The bladder filling rate was 50 ml/min. The patient was asked to indicate the first sensation of bladder filling, the first desire to void and the moment of a strong desire to void. Permission to void was then given. Post void residual volume was determined through the catheter. Next, the ENS was turned on with the stimulation amplitude just above the sensory threshold and the pulse width and frequency set at 210 usec and 14 Hz, respectively. The urodynamic study was then repeated (UDS 2). The patients were given antibiotics for three days to prevent urinary tract infections following the urodynamic study. After the urodynamic study, the standard procedure was resumed, that is, the patient completed a bladder

diary which was evaluated after one week. The PNE was considered positive if at least 50% improvement was obtained in at least one of the symptoms (frequency, voided volume or incontinence episodes). In case the PNE was inconclusive, a first stage tined lead placement test (FSTLP) was proposed in which the permanent lead is placed in one of the S3 or S4 foramens and is connected to an external stimulator. Stimulation parameters were the same as during PNE. This test phase has a duration of about one month and the evaluation of success is done on the basis of bladder diary results of at least three days, which is comparable to the PNE evaluation.

Outcome measures

Demographic data, data from bladder diaries and the results of the PNE and FSTLP, were extracted from the medical record (Table 1). The outcome measures were various UDS parameters as given in Table 2. The results of three different UDS were compared: UDS B (performed at baseline, prior to the PNE, as a part of our standard procedure of care), UDS1 (after the PNE, without stimulation) and UDS2 (after the PNE, with stimulation). During UDS B two filling - voiding cycles were performed. Of these two cycles, the data of the filling phase with the highest filled volume and the data of the voiding phase with the highest maximum flow rate were used in the current study.

Statistical analysis

All statistical analyses were done with the Wilcoxon rank test for non-parametric related samples, using SPSS version 24.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 10 female patients with a mean age of 59 (interquartile range 54-63) years were willing to participate and completed the study protocol, see Table 1 for patient characteristics. All patients had OAB for at least 2 years with proven detrusor overactivity on UDS B. All patients except for one (patient 9) also showed detrusor overactivity during UDS 1 and UDS 2. The PNE was positive in 4 patients, inconclusive in 4 patients and negative in 2 patients (patient 2 and 9). The 4 patients with an inconclusive result reported to feel stimulation during UDS 2 but lost sensation after 2 to 4 days, possibly due to displacement of the lead. An FSTLP was next done, with a positive outcome in all 4 patients. Consequently, a permanent neuromodulator was implanted in 8 patients.

Table 1. Patient characteristics

	N
Male/Female	0/10
Age during PNE, in years median (IQR)	59 (54 – 63)
Frequency/24 hours, median (IQR)	13 (11 – 15)
Nocturia episodes, median (IQR)	4 (2 – 6)
Incontinence episodes, median (IQR)	3 (1 – 5)
Pad use/24 hours, median (IQR)	3.5 (1 – 5)
Functional bladder capacity in ml, median (IQR) *	246 (125 – 400)
Overactive bladder	
- Wet	9
- Dry	1
Concomitant bladder problems	
- Mixed incontinence	3
Therapies before PNE	
- Pelvic floor muscle therapy *	4
- Anticholinergics	10
- TENS/PTNS *	4
- OnabotulinumtoxinA *	3

* data of one patient was incomplete
IQR = interquartile range, TENS: transcutaneous electrical nerve stimulation, PTNS: Percutaneous Tibial Nerve Stimulation, PNE: percutaneous nerve evaluation

The median UDS 1 and UDS 2 parameters of the positively responding 8 patients are shown in Table 2. No statistically significant differences were found between UDS parameters without stimulation (UDS 1) and with stimulation (UDS 2). Figure 1 shows UDS parameters during filling phase, three data points are shown; UDS at baseline, UDS directly after the PNE without stimulation (UDS 1) and UDS directly after PNE with stimulation (UDS 2). The lines represent the 8 positively responding individuals and their median. In the outcome parameter "bladder volume at first sensation" 4 lines are missing. These patients did not indicate when the first sensation was notified. UDS parameters of the voiding phase are shown in Figure 2. The maximum flow rate and the pressure at maximum flow rate did not change significantly comparing UDS 1 and 2, also shown in Table 2.

Table 2. UDS parameters of UDS 1 and 2.

	UDS 1	UDS 2	P value*
Filling phase			
Bladder volume at 1st sensation *IQR*	157 ml *(89 – 290)*	115 ml *(63 – 147)*	.854
Bladder volume at 1st DO *IQR*	184 ml *(110 – 300)*	179 ml *(125 – 340)*	.263
Highest DO pressure *IQR*	32 cmH2O *(21 – 35)*	32 cmH2O *(21 – 35)*	.574
Bladder capacity in ml *IQR*	175 ml *(79 – 518)*	190 ml *(160 – 364)*	.401
Micturition phase			
Maximum flow rate *IQR*	12 ml/s *(10 – 17)*	10 ml/s *(6 – 14)*	.462
Pressure at maximum flow *IQR*	31 cmH2O *(26 – 43)*	31 cmH2O *(27 – 39)*	.089

*Wilcoxon Signed Rank Test for non-parametric related samples
UDS = Urodynamic study
IQR = Interquartile range
DO = Detrusor Overactivity

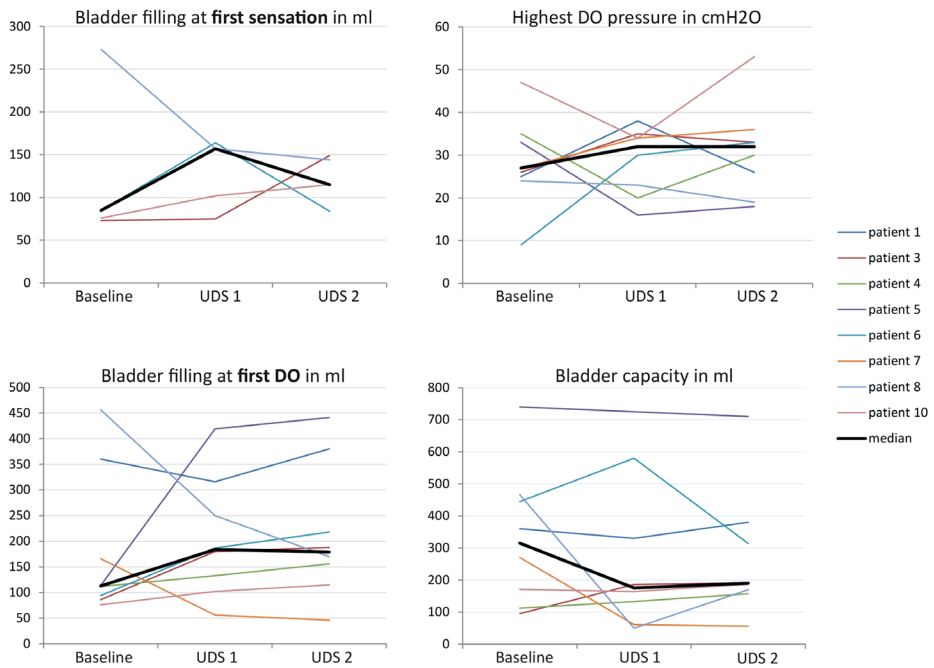

Figure 1. Urodynamic parameters of the filling phase of UDS B, UDS 1 and UDS 2.
Abbreviations: DO: Detrusor overactivity

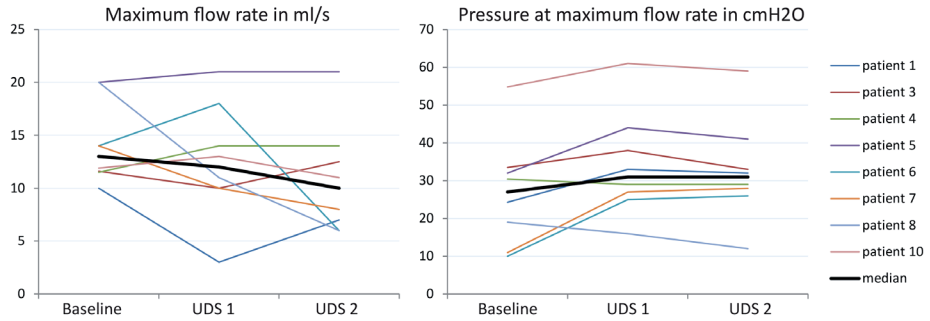

Figure 2. Urodynamic parameters of the voiding phase of UDS B, UDS 1 and UDS 2.

DISCUSSION

To our best knowledge, this is the first study that suggests that sacral neuromodulation has no significant acute effect on standard UDS parameters in patients with OAB in whom SNM is eventually an effective treatment. This accounts for both the filling phase and the voiding phase. The figures show that besides the median change of the parameters, the individual changes are also limited. These results are complementary to results of previous studies. Significant changes in UDS parameters were demonstrated after six months of SNM in patients with DO for both the filling and the voiding phase; the bladder volume at first sensation increased, the bladder capacity increased, the maximum detrusor pressure during the filling phase decreased and the Qmax increased.[22-24]

The working mechanism of SNM is still being investigated, but at present, it is believed that SNM activates afferent pathways modulating several brain areas which in turn regulate bladder control. Differences between acute and chronic SNM in regional cerebral blood flow (rCBF) have been demonstrated using PET.[7] When acute SNM is applied, brain areas predominantly involved in sensorimotor control, showed an increase in rCBF.[7] Moreover, during acute SNM, Blok et al. described a change of rCBF in the insula. These authors argued that this might cause activation of the sympathetic system, which, in turn, results in an increase in the bladder capacity.[7] The bladder capacity was not measured during this PET study. The current study did not demonstrate an increase in bladder capacity after acute SNM. In contrast to us, the study of Opisso et al. did show such an increase. They used subject-controlled dorsal genital nerve stimulation (DGN) in patients with neurogenic bladders due to partial spinal cord injury, multiple sclerosis or traumatic brain injury.[27] Subjects could turn on the stimulator as soon as they felt urgency during bladder filling. However, the underlying mechanisms of bladder dysfunction in neurogenic and idiopathic patients are not comparable.[28] In the present study only patients with idiopathic OAB were included.

During chronic stimulation, when SNM has been active for 6 months, changes in the rCBF in brain areas involved in attention and alertness were detected.[7] This, in turn, would result in less firing of the pontine micturition center (PMC) and restore bladder function. The fact that this rCBF change in the brain areas involved in attention and alertness is only detected after chronic SNM and not after acute SNM might be related to the working mechanism of SNM and could explain the differences in results in UDS between acute and chronic stimulation. The areas predominantly involved in sensorimotor control showed a decrease in rCBF after chronic stimulation, instead of the increase in rCBF after acute SNM. This change might also explain the differences in results in UDS between acute and chronic stimulation.

The wash out duration of SNM has been investigated. Cadish et al. found a mean of 11.25 days before return of symptoms after turning the SNM off in 12 women with OAB.[8] Altomare et al. detected that in 19 patients with urinary incontinence or fecal incontinence, the mean time to recurrence of symptoms after turning the SNM off was 3.4 months (range 0.9 – 13.5) and in 9 patients symptoms never returned.[9] In conclusion, chronic effects of SNM seem to be maintained some time after stimulation is stopped, suggesting neuroplasticity of the involved brain areas. Moreover, the onset of action of SNM was recently investigated using bladder diaries which indicated that the mean time to 50% or greater symptom improvement was 3.3 days.[29]

These results, and those of the current study, suggest that a closed-loop feedback system, which activates SNM automatically when the detrusor pressure increases, would not be effective due to lack of acute effects after such short stimulation. However, on-demand and intermittent neuromodulation have been proved to be effective therapies in two separate trials.[11,14] A possible explanation might be that in both trials, the patients were already using the SNM for > 7 years and 48 months, respectively.[11,14] The above described neuroplasticity of the involved brain areas might already have been utilized, indicating that hypothetically, these neuroplastic changes can be maintained by intermittent or on-demand neuromodulation. Suggestions for future research in the use of a feedback neuromodulation system would be to investigate it with patients who are long-term users and who are starting users of SNM.

The main limitation of the current study is its small sample size. We initially aimed at a larger sample size. However, considering the absence of statistically significant findings in 8 successfully tested patients and the invasiveness of the UDS, we decided to stop inclusion for ethical reasons. In 4 patients, the first sensation of bladder filling was not noted because they had an involuntary detrusor contraction followed by direct urine leakage and micturition. Four patients had undergone a FSTLP after the PNE because of inconclusive PNE results. This inconclusive PNE was most likely caused by lead migration as all 4 patients described a loss of sensation of stimulation of stimulation after some days. Lead migration is a known disadvantage of PNE compared to a FSTLP and might be

the cause that PNE is a less sensitive screening method than FSTLP.[30] In our hospital, OAB patients first undergo a PNE, in case this is inconclusive, a FSTLP is conducted. The influence of this on our study results is considered minimal, since all four patients reported to feel stimulation during the UDS 2 at the same location as during placement of the PNE lead. Moreover, the stimulation parameters used during PNE and FSTLP were the same (frequency 14 Hz and pulse width 210 μs). Ultimately, for this study, it was merely of relevance whether or not the patient is a responder to sacral neuromodulation in general. The method of testing is of secondary importance.

In conclusion, this study suggests that there are no acute effects of SNM on conventional UDS parameters. More studies are needed to confirm this finding and further elucidate the role of factors such as gender, age and etiology of OAB.

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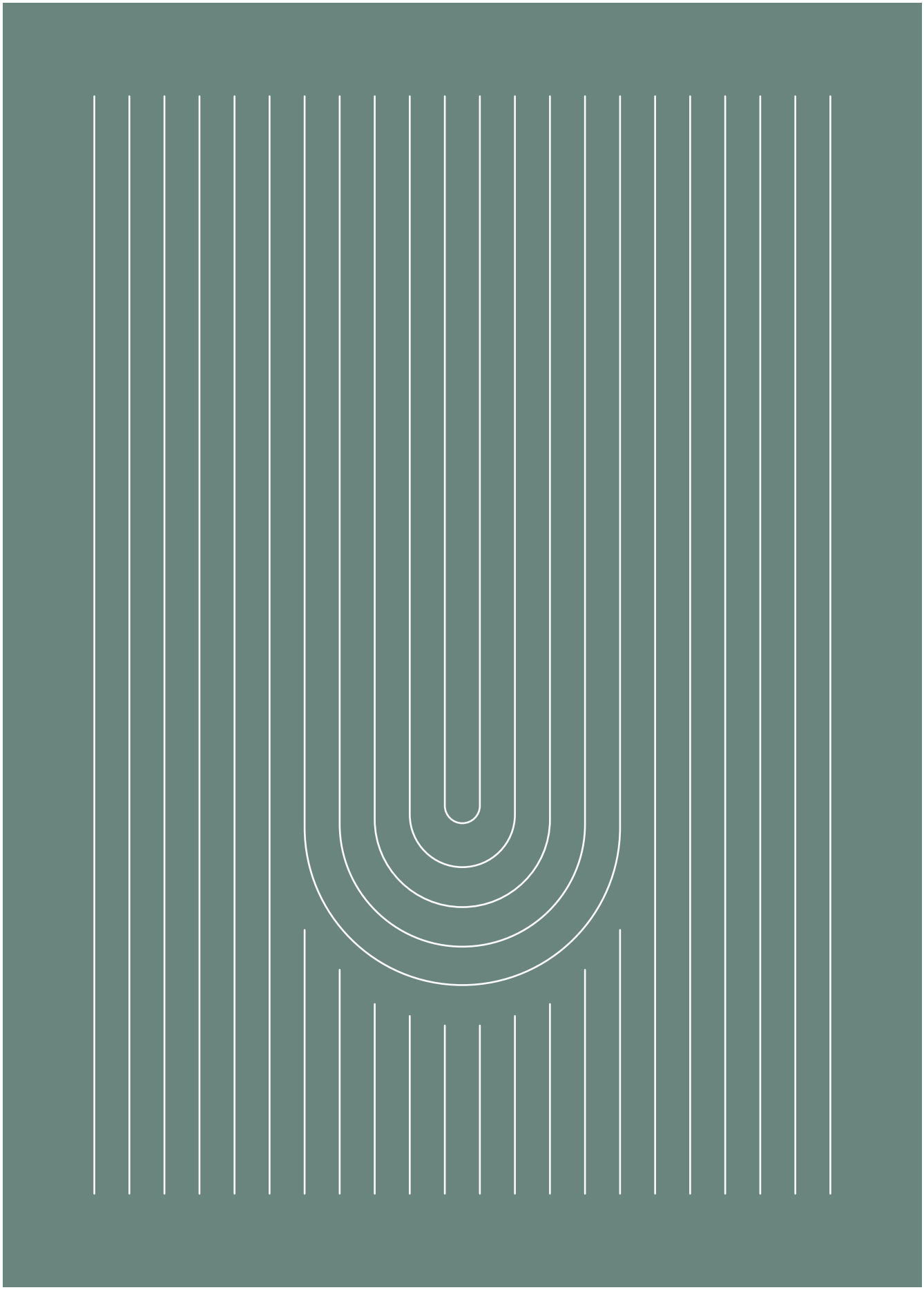

CHAPTER 6

The validation of the Dutch OAB-q SF: an overactive bladder symptom bother and health-related quality of life short-form questionnaire

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ABSTRACT

Aims: The OAB-q SF evaluates both symptom bother and health-related quality of life in patients with overactive bladder, a highly prevalent disease. The objective of this study was to translate and validate a Dutch version of the OAB-q SF.

Methods: The translation into Dutch and validation process of the OAB-q SF was performed according to standardized guidelines. Patients with overactive bladder who visited the department of Urology outpatient clinic completed the questionnaires OAB-q SF, EQ-5D-5L, UDI-6 and the ICIQ-OAB at baseline (test) and two weeks later (retest). A reference group from the department of Allergology outpatient clinic completed the same questionnaires once. The evaluated measurement properties included content validity, internal consistency, reproducibility, criterion validity and construct validity.

Results: Fifty-two patients were included in the study group and 51 references were included. The content validity was adequate and the internal consistency was excellent (Cronbach's alpha > 0.80). The reproducibility was good with intraclass correlation coefficients higher than 0.70. Patient's OAB-q SF scores were moderately to strongly correlated with the UDI-6, ICIQ-OAB and the EQ-5D-5L confirming the criterion validity. A good construct validity was demonstrated with significant higher scores of the OAB-q SF score in patients compared to references.

Conclusions: The Dutch OAB-q SF is a reliable and valid measure to evaluate symptom bother and health-related quality of life in patients with overactive bladder.

Keywords: Patient Reported Outcome, Questionnaire, Overactive Bladder, Urgency, OAB-q SF, Validation, Translation

INTRODUCTION

Overactive bladder (OAB) is defined as urgency, with or without urgency urinary incontinence, usually associated with frequency and nocturia. The prevalence of this condition is described to be between 13 – 16 % worldwide, and is expected to increase as a result of the aging of the population. It has been shown to have a great negative impact on an individual's health-related quality of life (HRQOL). All this causes a high burden on society.[1-3]

OAB is a symptom-based condition, with low positive and negative predictive values for urodynamic investigations.[4,5] The best method available to diagnose disease, quantify disease severity and evaluate treatment effects is therefore the use of patient reported outcome's (PROs), usually in the form of a questionnaire. Since the introduction of PROs, many different questionnaires have been developed. In order to compare the burden of OAB in patients and define guidelines for treatment, consensus is necessary on the specific questionnaire to use. The EAU (European Association of Urology) and the ICS (International Continence Society) guidelines do not recommend specific questionnaires to use for OAB, but both professional organizations mention that it is important to use questionnaires validated in the language of use.[6,7] The International Consortium for Health Outcome measurements (ICHOM) aims to improve value-based healthcare by defining global standard sets of outcome measures for different conditions. A core set of outcome measures for OAB which includes the OAB-q SF questionnaire, was developed in 2017.[8]

The OAB-q Short Form (SF) is a worldwide used questionnaire for health-related quality of life in patients with OAB. OAB-q SF is the shorter version of the 33-item "OAB-q" questionnaire. The OAB-q SF includes 19 items; a 6-item symptom bother scale and a 13-item health-related quality of life (HRQOL) scale.[9,10]

Before implementing the ICHOM set of outcome measures for OAB in the Netherlands, the OAB-q SF questionnaire needs to be translated and validated in Dutch. Therefore the aim of this study is to translate and validate the OAB-q SF in the Dutch language.

MATERIALS AND METHODS

Study design

This is a single-center, prospective cohort validation study, for which approval was obtained by the Ethics Review Board.

Patient group

All patients seen at the Urology outpatient clinic in between April 2018 and February 2019 diagnosed with OAB were eligible for screening. OAB was defined as urinary urgency, with or without urinary incontinence. Inclusion criteria were age ≥18 years and being fluent and literate in the Dutch language. Exclusion criteria consisted of urinary diversions, a history of/or active malignant tumors of the urinary tract, hematuria, bladder stones, neurogenic bladder, dementia, mental retardation and symptomatic urinary tract infection. The treating physician explained the study to patients eligible for inclusion and invited to participate. After signing informed consent patients were asked to complete the questionnaires during the inclusion visit (test) and 2 weeks later at home (retest). Characteristics of the included patients were extracted from the medical records.

Reference group

Patients who visited the department of Allergology outpatient clinic between September 2019 and December 2019 were invited as reference group. Inclusion criteria were age ≥18 years and being fluent and literate in the Dutch language. Exclusion criteria consisted of a urological medical history or current bladder problems, dementia and mental retardation. We considered these patients as a proper control group as allergy pathology has no relationship with bladder problems; those with bladder problems were indeed not eligible for inclusion in the reference group. Patients who met inclusion criteria were informed by their treating physician and if willing to participate, informed consent was signed and one set of questionnaires was completed.

Questionnaires

The questionnaire set included 4 questionnaires: the OAB-q SF, the EQ-5D-5L, the Urogenital Distress Inventory 6 (UDI-6) and the International Consultation on Incontinence Questionnaire Overactive Bladder (ICIQ-OAB).

- The OAB-q SF is a 19-item, self-administered disease specific instrument derived from the OAB-q.[9,10] The OAB-q SF contains two main subscales: Symptom bother (6 items) and Health Related Quality of Life (HRQOL, 13 items). Each item is rated on a six-point Likert scale, for the symptom bother scale ranging from 0 (not at all) to 6 (a very great deal) and for the HRQOL scale from 0 (none of the time) to 6 (all of the time). The two subscales are separately summed and, on the guidance of the

scoring manual,[9] transformed into scores ranging from 0 to 100. A higher score on the symptom bother scale indicates a greater symptom severity and a higher score on the HRQOL scale indicates a better HRQOL, so they are inversely related to each other. These two scores, are always be mentioned separately, since the OAB-q SF has no total score.

- The EQ-5D-5L questionnaire (European Quality of life 5-Dimension 5-Level questionnaire) developed by the EuroQol group, is one of the most used PRO instruments for the measurement of HRQOL.[11] It consists of 5 questions addressing mobility, self-care, activities, pain/discomfort and anxiety/depression, the answers are transformed to an index value ranging from 0 (inability) to 1 (no problems) by using the accessory index value calculator. In addition, the health state is self-reported by completing a visual analogue scale (VAS) ranging from 0 "the worst health you can imagine" to 100 "the best health you can imagine".
- The UDI-6 is a six-item symptom inventory, specific to symptoms associated with lower urinary tract dysfunction. It combines information on irritative, stress and obstructive/discomfort symptoms of the lower urinary tract.[12] This questionnaire has been translated and validated in Dutch and the mean score of the six items is converted to a 0-100 scale on the guidance of the scoring manual.[13]
- The ICIQ-OAB questionnaire indicates the symptom bother of frequency, nocturia, urge and incontinence in 4 questions. The impact on quality of life of these four problems is self-reported by completing four bother scales from 0 to 10. According to the design of the questionnaire the results of the ICIQ-OAB questions are summed creating a score; ICIQ-OAB Q questions. Furthermore, in the present study the bother scales are summed; ICIQ-OAB BS (bother scales), creating a value ranging from 0 to 40 indicating the HRQOL. The design of the questionnaire does not indicate how to calculate the total score of the bother scales.

Cross-cultural adaption

The cross-cultural adaption of the original English OAB-q SF into the Dutch language was done according to the standardized guidelines for linguistic validation.[14] The forward-translation of the English OAB-q SF into the Dutch OAB-q SF was performed by three professional native Dutch-speaking translators separately. During a consensus meeting discrepancies between the three translations were discussed with the translators, two urologists (BB and JS) and the primary investigator (IG). The final version (see supplementary material) was backward-translated by a native English-speaking translator. To confirm the content validity of the Dutch version, the questionnaire was evaluated face-to-face with 5 patients visiting the Urology outpatient clinic.

Measurement properties

Content validity

The content validity was assessed during the linguistic validation by patient and researchers (IG, BB and JS). Researchers subjectively evaluated the correspondence between the clinical symptoms of OAB and the questions. Patients reported on the formulation of the questions and clarity of the questions during the face-to-face evaluation.

Internal consistency

By assessing the correlation between different items within the questionnaire, the internal consistency is examined, demonstrating whether the items measure the same underlying construct. The Cronbach's alpha was calculated for the two subscales of the OAB-q SF. A Cronbach's alpha between 0.70 and 0.95 was considered to reflect adequate internal consistency.[15]

Reproducibility

The reproducibility is the degree to which repeated measurements in the test-retest period provide similar answers. When testing the reproducibility, a distinction between the reliability and agreement is made.[15,16] Reliability is determined by the degree to which patients can be differentiated from each other, despite the measurement error. This was expressed by the intraclass correlation coefficient (ICC) for agreement, scores over 0.70 are acceptable. Furthermore, the agreement indicates the measurement error which is the similarity in scores rated on separate occasions. The limits of agreement (LOA) were expressed as the mean change in scores of repeated measurements ±1.96 X standard deviation of the changes.[16,17]

Criterion validity

The criterion validity, i.e. the extent to which the OAB-q SF questionnaire scores relate to a gold standard, is determined with the Pearson's correlation coefficient (range -1 to 1) in case of a linear association and when a linear association is not seen, the Spearman correlation coefficient. For OAB, a gold standard does not exist, and instead the UDI-6 and the ICIQ-OAB (Q and BS) served as such.

Construct validity

Predefined hypotheses about the relation of the OAB-q SF to other instruments were tested. The construct validity is considered adequate when at least 75% of the results of predefined hypotheses are in accordance.[15] The following hypotheses were formulated:

1. The reference group will have lower OAB-q SF symptom bother scores and higher OAB-q SF HRQOL scores than the patient group.

2. Patients with a higher UDI-6 score will have a higher OAB-q SF symptom bother score.
3. Patients with a higher ICIQ-OAB Q (questions) score will have a higher OAB-q SF symptom bother score.
4. Patients with a higher ICIQ-OAB BS (bother scale) score will have a lower OAB-q SF HRQOL score.
5. Patients with a lower EQ-5D-5L index value and patients with a lower EQ-5D-5L VAS will have a lower score on the OAB-q SF HRQOL.

Floor and ceiling effects

Floor and ceiling effects were considered if more than 15% of the respondents would achieve the lowest or highest possible score.[15] The floor and ceiling effects were calculated for symptom bother and HRQOL scores at baseline in the patient and in the reference group.

Statistical method

A sample size of at least 50 participants was considered adequate for validation of questionnaires,[15] thus we aimed to include a total of 100 patients, 50 in the patient group and 50 in the reference group. Continuous data are presented as mean, standard deviation (SD). The Student's *t*-test and Chi-square test for continuous and categorical variables, respectively, were used evaluating differences between patient and reference group. Statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as *P*-Value <0.05.

RESULTS

In total, 103 participants were included in the study. In the patient group 56 patients signed an informed consent, of whom 52 patients completed the questionnaires at both time points. Four patients did not return the second questionnaire and were therefore excluded from the analyses. The reference group consisted of 51 participants who completed the questionnaires at one time point. Table 1 displays the patient characteristics and the baseline scores of the four questionnaires.

Table 1. Patient characteristics and baseline outcomes of measurements

	Reference group N = 51	Patient group N = 52	P-value
Age, yrs	41 (±15)	64 (±13)	*0.02*[a]
Gender			0.24[b]
Male	14 (28%)	20 (39%)	
Female	37 (72%)	32 (61%)	
Baseline scores			
OAB-q SF Symptom bother	12.4 ± 15.4	63.8 ± 21.6	*<0.001*[a]
OAB-q SF HRQOL	95.9 ± 5.4	50.9 ± 19.1	*<0.001*[a]
EQ-5D-5L index value	0.881 ± 0.156	0.738 ± 0.212	0.086[a]
EQ-5D-5L VAS	76.1 ± 14.3	71.7 ± 17.3	*0.043*[a]
UDI-6	8.9 ± 9.1	57.7 ± 20.7	*<0.001*[a]
ICIQ-OAB Q (questions)	2.3 ± 1.8	10.4 ± 2.9	*0.001*[a]
ICIQ-OAB BS (bother scales)	3.8 ± 6.3	29.4 ± 8.1	*0.037*[a]

[a]Student's *T*-test
[b]Chi square test

Content validity

Content validity was confirmed during the face-to-face evaluation of the questionnaire. Question 8 of the OAB-q SF HRQOL subscale was discussed, but did not lead to changes in the questionnaire. Furthermore, the face-to-face evaluation demonstrated that patients found the questionnaire understandable, easy to complete and clear.

Internal consistency

The internal consistency of the questionnaire was tested good for both subscales. Cronbach's Alphas between 0.70 and 0.95 reflect adequate internal consistency. In the patient group the OAB-q SF symptom bother subscale the Cronbach's Alpha scores were 0.84 and 0.87 for test and retest, respectively. For the OAB-q SF HRQOL subscale the Cronbach's Alpha were 0.88 and 0.91 for test and retest, respectively.

Reproducibility

In the patient group, the second questionnaire was returned after a mean of 15.8 days (SD ± 11). An adequate reliability was confirmed with ICCs higher than 0.70 for the two subscales of the OAB-q SF. Table 2 lists the ICCs for agreement and LOA ranges for the two subscales of the OAB-q SF.

Table 2. The reproducibility is presented in term of the intraclass correlation coefficient (ICC) and the limits of agreement (LOA)

	Change (mean ± SD)	ICC (95%CI)	LOA[a]
OAB-q SF symptom bother	-4.23 ± 13.89	0.79 (0.66 – 0.88)	-31.45 – 22.99
OAB-q SF HRQOL	2.37 ± 10.83	0.85 (0.76 – 0.91)	-18.84 – 23.58

[a]Calculated as : y= mean(change) ± 1.96 X standard deviation (change).

Criterion validity

Using Pearson's correlation coefficient a moderate to very strong correlation was detected between the OAB-q SF symptom bother and the UDI-6 and the ICIQ-Q. The criterion validity of the OAB-q SF HRQOL was evaluated by calculating the correlation with the IQIQ-BS and the EQ-5D-5L index values and VAS. Calculating the correlation with the EQ-5D-5L index values, the spearman correlation coefficient was used since no linear relationship was found between the OAB-q SF HRQOL and the EQ-5D-5L index value. Correlations demonstrated a weak to strong correlation (See Table 3 for Rho and *P*-values).

Table 3. Criterion validity measured using the Pearson's Correlation coefficient.

	UDI-6	ICIQ-Q	ICIQ-BS	EQ-5D-5L index value	EQ-5D-5L VAS
Test					
OAB-q SF Symptom bother	0.56 (<0.001)	0.84 (<0.001)			
OAB-q SF HRQOL			-0.67 (<0.001)	0.46 (<0.001)[a]	0.49 (0.001)
Retest					
OAB-q SF Symptom bother	0.72 (<0.001)	0.83 (<0.001)			
OAB-q SF HRQOL			-0.70 (<0.001)	0.43 (0.002)[a]	0.33 (0.016)

Values are Rho (P-value)

[a]Spearman's correlation coefficient because of nonparametric correlation.

Construct validity

All predefined hypotheses were confirmed:

1. The reference group did have lower OAB-q SF symptom bother scores and higher OAB-q SF HRQOL scores compared to the patient group (Table 1).
2. Patients with a higher UDI-6 score had a higher OAB-q SF symptom bother score (Table 3).
3. Patients with a higher ICIQ-OAB Q (questions) score had a higher OAB-q SF symptom bother score
4. Patients with a higher ICIQ-OAB BS (bother scale) score had a lower OAB-q SF HRQOL score (Table 3).
5. Patients with a lower EQ-5D-5L index value and a lower EQ-5D-5L VAS had a lower score on the OAB-q SF HRQOL (Table 3).

Floor and ceiling effects

In the patient group, no floor or ceiling effects were seen for the two subscales (Table 4). In the reference group, floor effects were seen for the symptom bother subscale; 17.6% scored the lowest possible score of 0. Moreover, in the HRQOL subscale, a ceiling effect was seen, in that 29.4 % of patients scored the highest possible score.

Table 4. Floor and ceiling effects at baseline.

	References N = 51		**Patients N= 52**	
	Floor (%)	**Ceiling (%)**	**Floor (%)**	**Ceiling (%)**
OAB-q SF Symptom bother	9 (17.6 %)	1 (2%)	0 (0%)	4 (7.7%)
OAB-q SF HRQOL	0 (0%)	15 (29.4%)	0 (0%)	0 (0%)

DISCUSSION

The primary aim of this study was to translate and validate the OAB-q SF in the Dutch language. The results of this study showed that this Dutch version is valid, reliable and consistent. This enables the use of the OAB-q SF in daily practice in the Netherlands. A valid tool to measure both symptom bother and health-related quality of life in patients with OAB in an easy and fast way.

The content validity of the questionnaire was confirmed during the face-to-face evaluation. Question 8 of the OAB-q SF HRCOL subscale was discussed. One patient commented on question 8 in the health-related quality of life subscale: 'During the past 4 weeks, how often have your bladder symptoms caused you to have problems with your partner or spouse?'. The issue was that response option 'not applicable' was lacking for those who had no partner. Because adding this response option would complicate the scoring manual, we discussed this problem with the designers of the original questionnaire.[9] In the cohort of Coyne et al, patients either leaved the question blank, and it was recorded as missing, or patients answer was 'None of the time' given that when it is not applicable, it really is none of the time. Therefor the Dutch version did not insert 'not applicable' as answer option, and no changes were made as a result of this discussion.[9] Moreover, according to the scoring manual of the OAB-q SF, the total score can be adapted to up to 50% of missing items, still creating a score ranging from 0 to 100.

The significantly different scores in the patient group (higher in symptom bother and lower in HRQOL) compared to the reference group, indicated a good discriminative ability and possible diagnostic value of the OAB-q SF. Comparable to the Cronbach's alphas of the original OAB-q SF (0.82 & 0.91) and the Spanish validation (0.81 & 0.92),[9,18] the Cronbach's alphas of the Dutch OAB-q SF were good (0.83 to 0.89), and demonstrated an excellent internal consistency. Using the change in scores between the test-retest, the

agreement and the limits of agreement were calculated, demonstrating an adequate reliability and reproducibility. These results are in accordance with the original OAB-q SF study,[9] and the Spanish validation study.[18]

Concerning the criterion validity, the present study used the UDI-6, the ICIQ-OAB and the EQ-5D-5L to correlate with the OAB-q SF because of the absence of a gold standard. As expected, the symptom bother subscale showed a strong correlation with the UDI-6 and the ICIQ-questionnaires for both test and retest. Moreover, the OAB-q SF HRQOL subscale showed a strong correlation with the ICIQ-bother scales, but the correlations with the EQ-5D-5L index value and EQ-VAS were moderate. The ICIQ-OAB bother scales are focused on OAB symptoms and the EQ5D5L is more in general, which might be a possible explanation for the moderate compared to strong correlation. The Spanish validation study also used the EQ-5D and -VAS and showed comparable, moderate correlations.[18] All predefined hypotheses in the present study were confirmed demonstrating that patients and references are well distinguishable, and therewith showing a good construct validity.

In the patient group, no floor and ceiling effects were detected, which implies that although many patients had severe OAB, the questionnaire is still discriminative enough to detect worsening or improvement of symptom bother or in HRQOL. In the reference group, as expected, a floor effect was found in the symptom bother scale (17.5%), indicating that in the reference group patients had no bother due to bladder problems. Moreover, a ceiling effect was seen in the HRQOL scale (29.4%), indicating that in the reference group, bladder problems were not severe enough or not present to create a decrease in HRQOL.

The strength of the current study is the use of standardized measurement properties as described by Terwee et al. to evaluate the reliability and validity of the OAB-q SF.[15] The current study did not determine the responsiveness and interpretability due to short follow-up, and a lack of therapy changes over time in the study group. This is a limitation of the study, however previous literature on the English OAB-q SF demonstrates a good responsiveness and interpretability.[9] There was a difference in the mean age between the patient and the reference group. The reference group is only used for one of the four hypotheses of the construct validity. All the other measurement properties are calculated without the use of the reference group, so without influence of this age difference. Another limitation of the study is the absence of a gold standard to assess the criterion validity. On the other hand, the absence of a gold standard in this highly prevalent disease demonstrates the need for a good PRO in OAB. The choice to implement the OAB-q SF in the ICHOM OAB-set suggests that this questionnaire might be a valid PRO for OAB symptoms.

Conclusion

In conclusion, this Dutch version of the OAB-q SF showed a good validity and reliability according to well established guidelines on measurement properties. The OAB-q SF is a suitable instrument for assessing both symptom bother and HRQOL in patients suffering from OAB. We recommend the use of this measurement tool in both research and clinical practice.

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Identificatienummer van de patiënt_____ Initialen van de patiënt _____

OAB-q SF - korte vragenlijst over de ernst van blaasklachten.

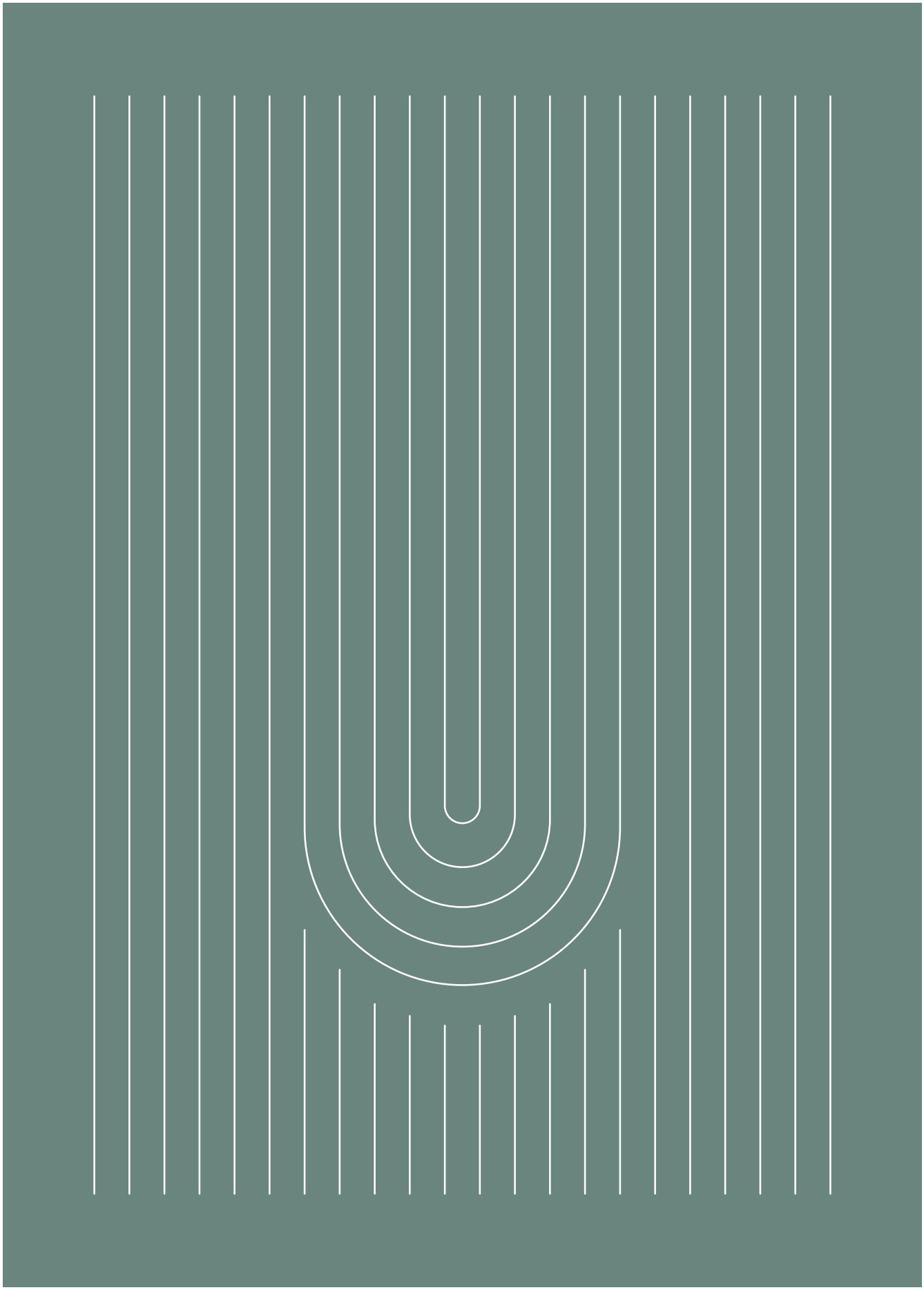
In deze vragenlijst kunt u aangeven hoeveel last u de afgelopen 4 weken heeft gehad van specifieke blaasklachten. Kruis het hokje aan dat het beste beschrijft in hoeverre u de afgelopen 4 weken last heeft gehad van elke klacht. Er zijn geen goede of foute antwoorden. Let erop dat u alle vragen beantwoordt.

Hoeveel last had u gedurende de afgelopen 4 weken van	**Helemaal niet**	**Een klein beetje**	**Enigszins**	**Nogal**	**Veel**	**Heel veel**
1. Een hinderlijke aandrang om te plassen?	☐	☐	☐	☐	☐	☐
2. Een plotselinge aandrang om te plassen met weinig of geen waarschuwing?	☐	☐	☐	☐	☐	☐
3. Ongewild verlies van kleine hoeveelheden urine?	☐	☐	☐	☐	☐	☐
4. ’s Nachts plassen?	☐	☐	☐	☐	☐	☐
5. ’s Nachts wakker worden omdat u moest plassen?	☐	☐	☐	☐	☐	☐
6. Urineverlies dat samengaat met een sterke behoefte om te plassen?	☐	☐	☐	☐	☐	☐

Identificatienummer van de patiënt_____ Initialen van de patiënt _____

Denk bij de volgende vragen aan uw algemene blaasklachten in de afgelopen 4 weken en hoe deze klachten uw leven hebben beïnvloed. Beantwoord elke vraag zo goed mogelijk over hoe vaak u zich zo voelde. Kruis het hokje aan dat de vraag het beste beantwoordt.

Hoe vaak hebben uw blaasklachten er in de afgelopen 4 weken toe geleid….	**Nooit**	**Heel soms**	**Soms**	**Vrij vaak**	**Meestal**	**Altijd**
1. Dat u “vluchtroutes” heeft gepland naar toiletten in openbare ruimtes?	☐	☐	☐	☐	☐	☐
2. Dat u het gevoel had dat er iets mis was met u?	☐	☐	☐	☐	☐	☐
3. Dat u geen goede nachtrust kreeg?	☐	☐	☐	☐	☐	☐
4. Dat u gefrustreerd of geïrriteerd raakte over hoeveel tijd u op het toilet doorbrengt?	☐	☐	☐	☐	☐	☐
5. Dat u activiteiten heeft vermeden omdat ze ver van een toilet af waren ? (bijv. wandelen of hardlopen)	☐	☐	☐	☐	☐	☐
6. Dat u ’s nachts wakker werd?	☐	☐	☐	☐	☐	☐
7. Dat u minder lichamelijke activiteiten heeft ondernomen? (beweging, sporten, etc.)	☐	☐	☐	☐	☐	☐
8. Dat u problemen kreeg met uw partner of echtgenoot/echtgenote?	☐	☐	☐	☐	☐	☐
9. Dat u zich tijdens het reizen met anderen ongemakkelijk voelde omdat u onderweg naar het toilet moest?	☐	☐	☐	☐	☐	☐
10. Dat het invloed had op uw relatie met familie en vrienden?	☐	☐	☐	☐	☐	☐
11. Dat u minder slaap kreeg dan u nodig had?	☐	☐	☐	☐	☐	☐
12. Dat u in verlegenheid werd gebracht?	☐	☐	☐	☐	☐	☐
13. Dat u bij aankomst op een onbekende plek meteen zocht naar het dichtstbijzijnde toilet?	☐	☐	☐	☐	☐	☐



CHAPTER 7

Long-term results of continent catheterizable urinary channels in adults with non-neurogenic or neurogenic lower urinary tract dysfunction

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ABSTRACT

Objectives: To evaluate the long-term results after the construction of a Continent Catheterizable Urinary Conduit (CCUC) in adults.

Methods: We retrospectively reviewed the charts of 41 adults from two tertiary centers who received a CCUC. The demographics, underlying diseases, indications for a CCUC and outcomes such as the reoperation rate and the occurrence of complications were extracted. The patient reported outcome was measured with the Patient Global Impression of Improvement (PGI-I) scale and four additional questions about continence, leakage and stomal problems.

Results: Twenty-nine patients were women. The median age at surgery was 32 years with a median follow-up of 52 months. Twenty-six patients had a neurogenic bladder. The reoperation rate was 48.8% with a median of 10.5 months after constructing the CCUC. Superficial stomal stenosis was the most common registered complication (20 times) and stoma revision was the most often performed reoperation (12 times). Twenty-four patients completed the PGI-I; the mean improvement rating was 2 (= much better).

Conclusion: The construction of a CCUC in adults is associated with a high complication and reoperation rate. The high reoperation rate is in accordance with the sparse literature. Despite this, patients reported "much better" on the PGI-I.

Keywords: Urinary diversion, Lower Urinary Tract Symptoms, Adults, Complications.

INTRODUCTION

Many patients with neurogenic or non-neurogenic lower urinary tract dysfunction are dependent on either clean intermittent catheterization (CIC) or an indwelling catheter for bladder emptying. Despite good instructions and feasible equipment, both approaches may give rise to problems such as urinary tract infection, pain and bleeding.[1-3] CIC requires a good dexterity, which may be challenging for people with spinal cord injury, especially those patient that are wheelchair bound. If management with CIC or an indwelling catheter affects a patient's quality of life too much, the alternative is to construct a continent catheterizable urinary channel (CCUC).[4] Mitrofanoff appendicovesicostomy and the Monti ileovesicostomy are the most often used catheterizable channels.[5-7] These procedures have been used in children and adolescents for more than three decades. Recently, our group showed that an appendicovesicostomy is an effective and durable solution for children when CIC is not feasible.[8] Little is known about the feasibility and risk factors for complications of CCUCs in adults. Publications so far show a wide range of complication rates and most cohorts included only patients with a neurogenic bladder dysfunction.[7,9-11]

The aim of this study was to evaluate the long-term results of CCUCs applied in adults and to identify possible risk factors for complications.

MATERIALS AND METHODS

The medical charts of 41 consecutive adults who had received a CCUC were retrospectively reviewed. Surgeries had been performed by three different experienced urologists, between November 1998 and November 2016 at the Erasmus University Medical Center, Rotterdam and at the University Medical Center Groningen, Groningen. The procedures used were those described by Mitrofanoff or Monti.[5,6] A Stoma was constructed either in the umbilicus with a V-shaped skin flap or in the right lower abdomen. A catheter was placed in the constructed stoma. Three to six weeks later the catheter was removed and the patient started with CIC. Follow-up was initially every 3 to 6 months, but the time interval was extended up to a year if bladder function remained stable and catheterization proceeded without problems.

After obtaining approval by the local ethics committee (MEC-2017-354), all patients who were still using the channel by the end of December 2017 were sent a 5-item questionnaire. The first question was the global impression of improvement (PGI-I instrument). 1) The PGI-I is a single question to rate the urinary tract condition now, as compared to before beginning treatment (construction of the CCUC) on a scale from 1: Very much better, to 7: Very much worse. The other questions were addressing 2) continence of the stoma (com-

pletely dry/some leakage, 1 pad is enough/ leakage with need for a stomal bag/stoma is completely incontinent/catheter in stoma), 3) urethral leakage (did you have any urethral incontinence the last two weeks? Yes/no), 4) difficulty with catheterization (always easy/ most of the time easy, sometimes not easy or painful/ always problematic or painfull), and 5) willingness to recommend this procedure to others with a comparable condition.

Demographic data extracted included patients' sex, age, body mass index (BMI) at time of surgery, length of hospital stay, underlying disease and the indication for a CCUC. Number of reoperations and the occurrence of complications served as outcome measures.

Stenosis was sub-divided in to cutaneous/fascial stenosis (superficial stenosis) and stenosis at conduit-bladder level (deep stenosis), stenosis was considered as a complication if a dilatation or a reoperation was needed, and the stenosis could not be resolved by minimally invasive therapies like ACE-stoppers or night-time catheters. Stomal or urethral urinary incontinence (UI) was considered a complication if reoperation was considered or patient could not properly absorb the leakage with incontinence material. Stomal pain during CIC was considered a complication if the patient had visited the emergency room or the outpatient clinic because of problems with CIC caused by pain or had been hospitalized for this reason. Urosepsis was considered as a complication when the patient was hospitalized for this reason. Stoma related reoperations were either stoma revisions (superficially), conduit revisions (including re-implantation of the conduit into the bladder), channel replacement (Mitrofanoff-channel to monti-channel, or monti-channel to a new monti channel), closing of the channel, using bulking agent at stoma level or augmentations. The use of a bulking agent in the urethra and dilatation of the stoma under general anesthesia were also registered but not as a stoma related reoperation.

Statistical analyses were performed with the statistical package SPSS statistics 24. Non-normally distributed variables are presented as median (interquartile range). Tests for normality were performed using the Shapiro-Wilk test. Non-parametric and Chi-square tests were performed to analyze risk factors (age and BMI) for reoperation. A *P*-value of < 0.05 was considered as statistically significant.

RESULTS

Table 1 shows patient demographics and diagnoses. The median follow-up was 52 months, with an interquartile range (IQR) from 19 to 120 months. The underlying diagnosis was neurogenic bladder in 26 patients (63%) and non-neurogenic bladder in 15 patients (37%). Concomitant surgery was performed in 24 patients; ileocystoplasty was the most common performed concomitant surgery (n=16). Bladder outlet procedures like bladder neck surgery or a bladder neck sling were performed in 6 patients. Two patients received onabotulinumtoxinA injections per-operatively. The stoma was placed umbilically in 35 (85%) cases. In 6 (15%) cases the stoma was placed in the right lower abdomen

Table 1. Patient demographics.

Patients	**N = 41**
Sex (%) Male / female	12 (29) / 29 (71)
Age at surgery in years, median (IQR)	32 (23 – 49)
BMI, median (IQR), 14 missing	25 (22.6 – 31.4)
Length of follow-up in months, median (IQR)	52 (19 – 120)
Bladder capacity pre-surgery in ml, median (IQR), 8 missing	400 (250 – 500)
Hospital stay days after surgery (range), 1 missing	10 (6 – 14)
Diagnosis/underlying diagnosis	
Neurogenic bladder (%)	**26 (63)**
Meningomyelocele	11 (27)
Spinal cord injury/cerebral contusion	7 (17)
Multiple sclerosis/other muscle disease	3 (7)
Polyneuropathy	2 (5)
Cerebral palsy	2 (5)
Pelvic injury	1 (2)
Non-neurogenic bladder (%)	**15 (37)**
Idiopathic bladder retention	4 (9)
Severe urethral strictures	3 (7)
Bladder-pain syndrome	1 (2)
Ehlers-Danlos syndrome	1 (2)
Prune-Belly syndrome	1 (2)
Other	5 (12)
Indication construction CCUC	
Neurogenic bladder (%)	**26 (63)**
Urethral leakage despite urethral CIC	7 (17)
Reduced dexterity	6 (15)
CIC while in a wheelchair	4 (10)
Urethral stricture's/fistula's by CIC	4 (10)
Pain during CIC	2 (5)
Other	3 (7)
Non-neurogenic bladder (%)	**15 (37)**
Pain during CIC	5 (13)
Reduced dexterity/hand/shoulder	4 (10)
Urethral strictures	3 (7)
CIC while in a wheelchair	1 (3)
Other	2 (5)
Type of surgery (%)	
Mitrofanoff	24 (59)
Monti-channel	17 (41)

Abbreviations: IQR; interquartile range, CIC; clean intermittent catetherization.

Patients with neurogenic bladder (n=26)

Underlying diagnoses and indications are shown in table 1. One patient showed no bladder activity during urodynamic evaluation after severe traumatic pelvic injury.

Patients with non-neurogenic bladder (n=15)

Underlying diagnoses and indications are shown in table 1. Furthermore, one patient had severe dysfunctional voiding with residual micturition and progressive kidney insufficiency. One patient had a conversion disorder, three other patients had a hypocontractile bladder.

Complications and reoperations

The overall reoperation rate was 48.8% (n=20) with a median of 10.5 months (IQR 4.5 – 30.8) after constructing the CCUC. This concerned 13 patients (50%) with neurogenic bladder and 6 patients (40%) with non-neurogenic bladder. There was no difference in the amount complications between the two centers.

From all complications superficial stenosis was by far the most common registered complication (20 times), followed by stomal incontinence (10 times). Stenosis at conduit-bladder lever occurred 4 times and stomal pain was considered a complication 3 times. Urosepsis occurred 3 times and urethral incontinence occurred twice. Stoma revision was the most performed reoperation (12 times) followed by conduit replacement (6 times). Complications and reoperations of patients with a neurogenic bladder are detailed in table 2, complications and reoperations of patients with a non-neurogenic bladder are detailed in table 3. Complications and reoperations could occur more than once in a patient.

Factors of influence

Factors potentially influencing the reoperation rate were analyzed. The probability of reoperation was significantly higher for patients above the age of 32 years compared with younger patients (Chi-square test p=0.043).

For BMI above or under the median BMI of 25, the Chi-square test was not statistically significant (p=0.431). BMI was missing in 14 cases.

Questionnaire

The questionnaire was sent to 32 of the 41 patients. Reasons not sending the questionnaire to 9 patients were: the stoma had already surgically been closed (n=4), permanent catheter in the stoma (n=2) and death, unrelated to the CCUC (n=3). The response rate was 24/32 (75%) of which 5 were males, the rest were females. The median PGI-I rating was 2 (much better) and all but two of the patients who had returned the questionnaire (22/24) would recommend this surgery to others in a comparable situation. See table 4

Table 2. Complications and reoperations in neurogenic bladder patients.

Pt. nr	1st complication	Time to 1st	2nd complication	Time to 2nd	3th complication	Time to 3th	Tot. FU
1	Deep stenosis → **Channel replacement**	3	-	-	-	-	99
2	Urosepsis	0	Urosepsis	3	Stomal UI → **Closing channel**	3	3
3	Stomal UI	28	† (not related to CCUC)	-	-	-	na
6	Sup stenosis	12	-	-	-	-	54
9	Deep stenosis → **Channel replacement**	2	Stomal UI → permanent catheter in stoma	8	-	-	8
10	Sup stenosis → **Closing channel**	8	-	-	-	-	38
11	-	-	-	-	-	-	35
13	Severe stomal pain	20	-	-	-	-	33
15	Deep stenosis → **Channel replacement**	11	-	-	-	-	27
16	Sup stenosis → **Stoma revision**	25	-	-	-	-	50
21	-	-	-	-	-	-	231
22	Sup stenosis → **Channel replacement**	3	Stomal UI → **Conduit revision**	9	Sup stenosis → **Dilatation**	41	227
23	Stomal UI → **B-A**	47	-	-	-	-	183
25	Sup stenosis	2	Urethral UI → **B-A**	10	Sup stenosis → **Channel replacement**	27	71
26	Urethral UI → **B-A**	78	† (not related to CCUC)	96	-	-	90
28	Sup stenosis → **Stoma revision**	37	-	-	-	-	67
29	Sup stenosis → **Dilatation**	-	-	-	-	-	15
31	Sup stenosis → **Stoma revision**	0	Deep stenosis → **Channel replacement**	2	-	-	123
33	-	-	-	-	-	-	219
34	Sup stenosis → **Stoma revision**	4	-	-	-	-	120
35	-	-	-	-	-	-	46
36	Sup stenosis → **Stoma revision**	11	Urethral UI → **B-A**	22	-	-	159
38	-	-	-	-	-	-	175
39	-	-	-	-	-	-	217
40	-	-	-	-	-	-	164
41	Sup stenosis → **Stoma revision**	27	Sup stenosis → **Stoma revision**	53	Sup stenosis → **Stoma revision**	111	155

Time to 1st/2nd/3th complications in months. **Bold** = reoperations, † = deceased. Abbreviations: CCUC; continent catheterizable urinary channel, B-A; Bulking agent, Tot. FU; total follow-up duration in months, UI; urinary incontinence, na; not available, sup stenosis: superficial stenosis = cutaneous/fascial stenosis, deep stenosis = stenosis at conduit bladder level.

Table 2. Complications and reoperations in neurogenic bladder patients. Time to 1st/2nd/3th complications in months. **Bold** = reoperations, † = deceased. Abbreviations: CCUC; continent catheterizable urinary channel, B-A; Bulking agent, Tot. FU; total follow-up duration in months, UI; urinary incontinence, na; not available, sup stenosis: superficial stenosis = cutaneous/fascial stenosis, deep stenosis = stenosis at conduit bladder level.

Table 3. Complications and reoperations in non-neurogenic bladder patients.

Pt. nr	1st complication	Time to 1st	2nd complication	Time to 2nd	3th complication	Time to 3th	Tot. FU
4	Severe stomal pain	2	† (not related to CCUC)	-	-	-	64
5	Stomal UI	28	-	-	-	-	71
7	Deep stenosis	33	-	-	-	-	46
8	Severe stomal pain	1	Stomal UI → **Conduit revision**	2	Severe stomal pain → **Closing channel**	14	14
12	Stomal UI → **Augementation**	5	-	-	-	-	33
14	Sup stenosis → **Stoma revision**	18	-	-	-	-	32
17	-	-	-	-	-	-	22
18	Stomal UI → **Stoma revision**	6	Sup stenosis → **Closing channel**	7	-	-	12
19	-	-	-	-	-	-	17
20	Stomal UI → permanent catheter in stoma	3	-	-	-	-	3
24	-	-	-	-	-	-	47
27	Sup stenosis → **Stoma revision**	35	Sup stenosis → **Conduit revision**	48	Urosepsis	73	89
30	-	-	-	-	-	-	72
32	-	-	-	-	-	-	100
37	Sup stenosis → **Stoma revision**	64	-	-	-	-	124

Time to 1st/2nd/3th complications in months. **Bold** = reoperations, † = deceased. Abbreviations: CCUC; continent catheterizable urinary channel, B-A; Bulking agent, Tot. FU; total follow-up duration in months, UI; urinary incontinence, na; not available, sup stenosis: superficial stenosis = cutaneous/fascial stenosis, deep stenosis = stenosis at conduit bladder level.

Table 3. Complications and reoperations in non-neurogenic bladder patients. Time to 1st/2nd/3th complications in months. Bold = reoperations, † = deceased. Abbreviations: CCUC; continent catheterizable urinary channel, B-A; Bulking agent, Tot. FU; total follow-up duration in months, UI; urinary incontinence, na; not available, sup stenosis: superficial stenosis = cutaneous/fascial stenosis, deep stenosis = stenosis at conduit bladder level.

for other questionnaire results. Of the 10 patients who answered "some leakage from the stoma, but 1 pad is enough", 4 had undergone a concomitant ileocystoplasty during construction of the CCUC. Of the 9 patients with some urethral incontinence, 5 patients (all female) had undergone a concomitant ileocystoplasty.

Table 4. Questionnaire results. Abbreviations: PGI-I; patient global impression of improvement.

	N = 24
PGI-I	
1. Very much better	9
2. Much better	8
3. A little better	3
4. No change	1
5. A little worse	2
6. Much worse	1
7. Very much worse	0
Continence stoma	
Dry	11
Some leakage, pad enough	10
Incontinent/catheter/other	1/1/1
Continence urethra	
Yes	9
No	15
Catheterization stoma*	
Always easy, no pain	9
Easy, sometimes problematic	10
Most of the time problematic	2
Always problematic	2
Would you advise this surgery to others?	
Yes	22
No	2

*Catheterization stoma: 1 missing

DISCUSSION

Twelve of 41 patients had remained entirely complication-free after the construction of a CCUC for different indications. The other 29 patients presented with superficial stomal stenosis, stomal or urethral UI, stenosis at conduit-bladder level, pain or urosepsis and 20 of them needed at least one reoperation. Furthermore, the perceived improvement was 'much better' and 22 of 24 patients would recommend this surgery to others. Effective patient counseling before constructing a CCUC is important, as shared decision

making is only possible when the patient is aware of the possible complications and the probability of reoperation.

The applicability of a CCUC in adult patients with lower urinary tract dysfunction remains questionable. An important consideration is the lack of other options when quality of life is affected by painful CIC, difficulty in performing CIC, urinary tract infections or problems with indwelling catheters. An alternative might be an incontinent urinary diversion (Ileum conduit), but this type of surgery is more invasive and also known for its complications. Most patients would prefer a continent stoma.[12]

Table 5. Overview of the published literature.

Author	Year	Patients N/NN	Follow-up	Age	Continence	Stenosis	Re-operation
Current study	2019	26/15	52 M (19–120)	32 Y (23–49)	88%	46%	49%
Perrouin-Verbe et al.	2016	29/0	66 M (50-80)	35 Y (26-46)	100%	6%	24%
Rey et al.	2013	11/4	22 M (9-33)	32 Y (22–65)	-	-	20%
Van der Aa et al.	2009	12/23	62 M (6–117)	44 Y (21–80)	75%	29%	54%
Sahadevan et al.	2008	7/22	10.5 Y (0.4–16)	48 Y (18–79)	89%	57%	49%
Touma et al.	2007	12/0	2.8 Y (0.25–5.8)	27 (14–50)	-	-	-
Karsenty et al.	2007	12/0	44 M (20–56)	42 Y (18–63)	100%	-	0%

N = neurogenic bladder, NN = non-neurogenic bladder, M = months, Y = year.

The reoperation rate of 48.8% we found falls within the range reported in the sparse literature (detailed in table 5).[10,13-17] Studies on predicting factors for complications have shown contradictory results. In a study by De Ganck et al. in 53 patients (mean age 19 years, SD 13), multiple regression analysis showed no association between the complication/follow-up ratio and age.[15] In contrast, Sahadevan and colleagues described a significantly increased incidence of stomal complications in 29 patients aged > 50 years.[14] A recurrent point of discussion is the heterogeneity of the studied populations, making a balanced comparison challenging.[11] Together with low numbers of patients, statistical analysis to find predicting factors for complications or reoperation is difficult. We found a significantly increased risk on reoperations for patients above the age of 32 at the time of surgery. This finding should be interpreted with caution, as duration of follow-up may be a confounding factor. A high BMI has not yet been identified as significant risk factor for stomal complications in patients with a CCUC, which could be due to the small patient samples studied. However BMI is reported as risk factor for complications in many other types of stoma, for example colorectal stoma.[18] Moreover, in patients with a myelomeningocele or other spinal cord diseases, the BMI might not be a good predictive parameter for the amount of abdominal fat, because BMI is not taking the underdeveloped muscles in the legs of these patients in to account. In essence, all this information could be helpful for the urologist and the patient to decide on constructing

a CCUC or not. Nine patients were, at the time of data collection, not using their CCUC anymore. Hopefully, this study contributes to make a better patient selection.

Besides the patient-related risk factors, other factors might influence the risk of complications, such as the quality of pre- and post-operative care. This quality can be enhanced by the availability of a specialized nursing team creating optimization of instructions and practice of self-catheterization.

One of the strengths of this study is the use of a questionnaire, which provided more insight in patients' opinions, which appeared positive despite the high reoperation rate. Obvious limitations include the limited patient numbers and the retrospective character of the collected data. Furthermore, we did not send the questionnaire to the patients who did no longer use the CCUC and had received new treatments. Therefore, the questionnaire results on the use of the CCUC may have been biased to some extent, and these results may be questioned. Nine out of 24 patients stated that they had some urethral leakage during the past two weeks. Five of these had undergone a concomitant ileocystoplasty, all females. We cannot differentiate between a preexistent stress urinary incontinence or an incontinence due to a low capacity based on this question. Bladder capacity was measured using urodynamics in every patient before the construction of a CCUC, and an ileocystoplasty was constructed if the bladder capacity was low.

In conclusion, the construction of a continent catheterizable urinary channel in adults comes with a relatively high number of complications, no risk factors could be identified yet. In the context of shared decision making, both the urologist and the patient should carefully consider the risk of failure of the constructed CCUC, the reported results of the questionnaire and the paucity of other options. Prospective studies with larger cohorts will be needed to identify predicting factors for complications.

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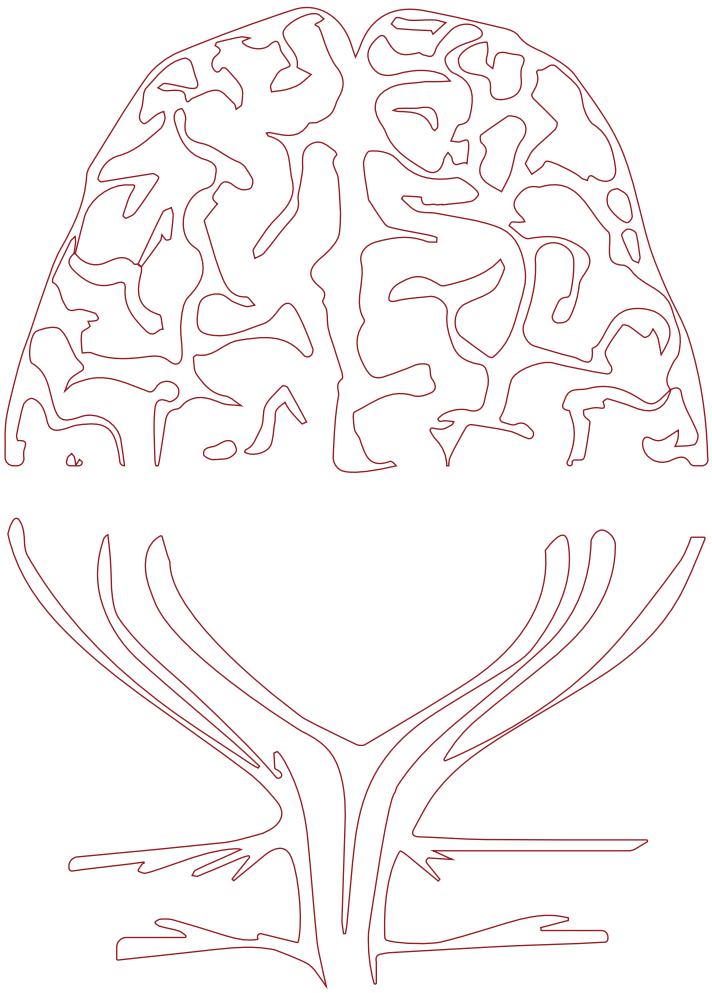
Disclosure of interest: The authors report no conflict of interest.

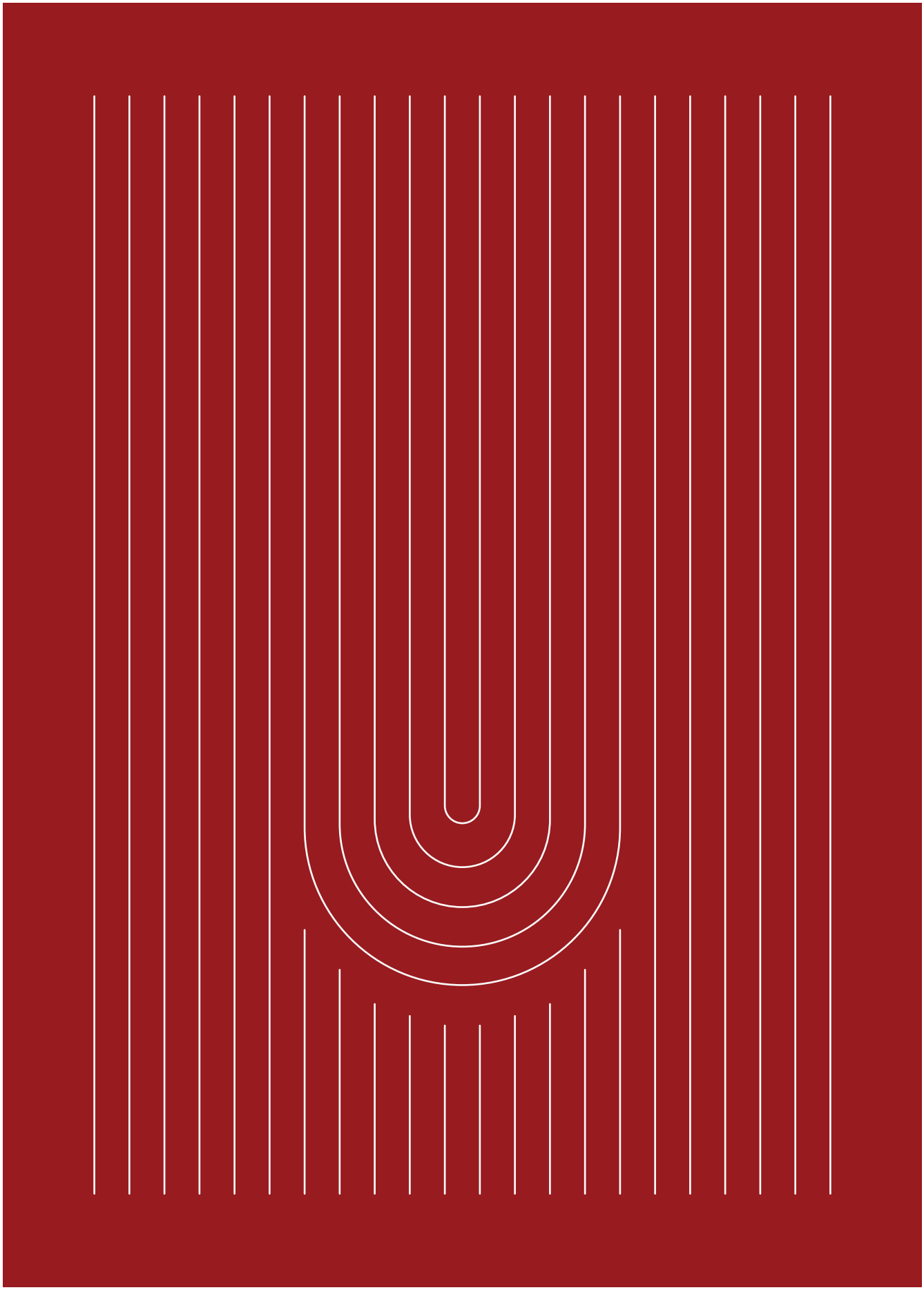
Ethical approval: The local ethics committee approved this study(MEC-2017-354).

Informed consent: All patients who filled in questionnaires gave written consent. Participation in the study was voluntary and anonymous with no explicit incentives provided for participation.



PART III

GENERAL DISCUSSION AND SUMMARY



CHAPTER 8

General discussion and future perspectives

In the field of functional urology, the availability of outcome parameters is limited. At present, the main outcomes are related to the subjective symptom perception of the patient. Due to the lack of outcome parameters, progress in scientific and clinical research in the field of functional urology might be obstructed. In this thesis, we attempted to expand the knowledge on (patho)physiology, identifying objective outcome measurements, improving subjective outcome measurements in the form of patient reported outcome measurements (PROMS), and contribute to the development of prediction models towards personalized care in functional urology.

DYNAMIC BRAIN IMAGING: A FUTURE DIAGNOSTIC TOOL IN FUNCTIONAL UROLOGY?

In the first part of this thesis we focused on the innervation of the lower urinary tract (LUT) and investigated the possible use of dynamic brain imaging as objective outcome measurement in clinical practice.

1. Do we know which brain areas are of interest when investigating the LUT?

The evolution of dynamic brain imaging generated an increase in knowledge on the innervation of the LUT.[1-5] Still, there is no consensus on which brain areas are involved in central LUT control.[6] Several properties of the acquisition and processing of dynamic brain imaging, make it hard to summarize the available data. Examples of these properties are the heterogeneous characters of the tasks performed in the MRI scanner (for instance different ways of bladder filling), the heterogeneous scan paradigms (for instance length and repetition of tasks), mixed genders, mixed patient populations as well as differences in used techniques (PET/1.5T fMRI/3T fMRI). A coordinate-based meta-analysis can be used to create a comprehensive overview of the relevant brain areas. A widely accepted method for coordinate-based meta-analysis is the activation likelihood estimation (ALE) which uses the inserted coordinates as a spatial probability distribution. In **chapter 2**, an ALE analysis using all published data on this topic indicated which brain areas are involved in the motor control of the LUT, divided into pelvic floor muscle contraction and micturition. The shortage of available data necessitated us to perform the ALE analysis with a lenient threshold; the results should thus be interpreted with caution. The results of this chapter are, to the best of our knowledge, the first results on motor innervation of the LUT investigated in more than 100 patients.

The brain areas that showed to be involved are in accordance with the findings of other relevant systematic reviews (without meta-analysis), although most literature focused on bladder control and not on pelvic floor muscle control.[6-9] We have demonstrated that two different motor tasks of the LUT, are innervated by distinct brain areas.

A previous study used ALE analysis in 181 patients to demonstrate which brain areas are involved during bladder filling, which is the main sensory task of the LUT.[10] Bladder filling has often been studied, whereas the somatosensory representation of the genitals has rarely been investigated.[11-14] Data seem not yet sufficient to perform a meta-analysis on the somatosensory representation of the external genitalia. The 7T fMRI study presented in **chapter 3** showed which brain areas are involved in pelvic floor muscle contractions in healthy individuals. The 7T fMRI study presented in **chapter 4** demonstrated which brain areas are involved in the individual processing of sensory information of male genitals in healthy individuals. The findings of **chapters 2, 3 & 4**, increased the knowledge on the involved brain areas in the central motor and sensory control of the LUT. This basic knowledge about the central control of the LUT is essential for the use of fMRI in individual patients in clinical practice.

2. Are the activity patterns divergent between patients and healthy subjects?

The further applicability of dynamic brain imaging to study the control of the LUT depends on clinical validation of the differences observed in outcomes between different populations, i.e. healthy persons versus patients and between patients before and after therapy. Research has demonstrated on group level that the results of dynamic brain imaging are different between patients and healthy subjects, and before and after therapy. Several brain areas, such as the supplementary motor area, the cingulate gyrus and the prefrontal cortex, have been described to be of interest when studying these differences.[15-20] At present, it is still unclear whether the differences between patients and healthy individuals and before and after therapy are detectable on individual level.

3. Is this 'tool' eligible for studying the LUT in individuals?

Single subject results obtained with the use of ultra-high field imaging regarding more basic tasks (e.g. digit somatotopy) have been found complementary to group results.[21, 22] Results on individual level for the LUT are scarce, however, which is at least partly related to the suspected inter-individual differences caused by the affective involvement in these tasks.[23] In the studies presented in **chapters 3 & 4,** activity patterns of individuals were analyzed using 7T fMRI to investigate whether in relation to the motor and sensory innervation of the LUT these patterns are comparable to group results. Both studies demonstrated that 7T fMRI is a feasible technique to study LUT whole-brain activity patterns at single-subject level.

4. Do we need ultra-high field imaging?

In previous studies using 1.5T and 3T fMRI, demonstrating individual results was uncommon as these results would not have a spatial acuity that allows for interpretation of individual results.[23] At 7T, signal-to-noise ratios and blood-oxygenation-level-dependent

signals have higher sensitivity, thereby increasing the spatial resolution.[24] Studies comparing results obtained at 3T with results obtained at 7T demonstrate relevant differences.[22,25] These studies are suggesting that the increase in resolution at 7T allows for interpretation of individual results. The above-mentioned arguments demonstrate ultra-high field (7T) imaging should be preferred for implementation of fMRI in clinical practice.

5. Is 7T fMRI available in clinical practice in the future?

The main drawbacks of 7T, compared to 1.5/3T, are the susceptibility for motion artefacts and some specific technical problems. For example, in 4 out of 17 patients included in **chapters 3 & 4**, the data could not be used due to motion artefacts. Furthermore, at present, data processing methods are relatively time consuming. These issues might diminish as the technique of high field imaging is evolving. Moreover, the safety of 7T in patients with implantable devices still has to be demonstrated.[26] Lastly, 7T MRI scanners are limitedly accessible and their use as diagnostic in clinical practice is therefore still very rare. In the Netherlands, three 7T scanners are available and these are mainly used for scientific purposes. The costs of such investment in hospitals are considerable, which might impede the implementation of 7T in clinical practice.

In conclusion, we further defined the involved brain areas in the central control of the LUT and the present results suggests that ultra-high field fMRI is an eligible tool in individuals. Thus, 7T fMRI might be suitable as a future 'diagnostic tool' in the field of functional urology. Some important issues need to be addressed before this technique can be implemented in clinical practice. First, gathering more fMRI data on both healthy individuals and patients is necessary to define the pathophysiology of diseases in the field of functional urology and to specifically delineate the differences in the results of fMRI between patients and healthy individuals. Standardized protocols for, i.e. bladder filling tasks, pelvic floor muscle contraction tasks and micturition tasks appear relevant to decrease the heterogeneity between studies. Furthermore, this high-field imaging technique is time consuming and limitedly accessible, issues that might diminish with the evolution of this technique.

IMPROVING TRADITIONAL AND PATIENT REPORTED OUTCOME MEASUREMENTS IN FUNCTIONAL UROLOGY

A future perspective is the creation of a prediction model that includes patient characteristics and (objective and subjective) outcomes to personalize the management of diseases in the field of functional urology. Such model might increase the success rates

of therapies. Furthermore, it might save time and healthcare costs and could reduce symptom bother and needless side effects of insufficient therapies.[27] To realize such a personalized management tool, the amount of data on patient characteristics, diseases, outcomes, patient reported outcome measurements (PROMS) and risk for complications needs to increase and the quality of the data needs to improve. In the second part of this thesis we aimed to evaluate and improve traditional outcomes and PROMS.

Improvement of the use of objective outcomes in functional urology

An objective outcome in the field functional urology is a urodynamic study. It measures several parameters in context of bladder function during both the filling and voiding phase, like bladder capacity, compliance and contractility.[28] Previous studies have investigated whether urodynamic parameters in patients with overactive bladder are predictive for the chance of success upon sacral neuromodulation (SNM). A significant relation between urodynamic parameters and outcomes of the test phase for SNM has not been demonstrated.[29,30] Nevertheless, significant changes on urodynamic parameters were seen during SNM therapy > 6 months.[31,32] The objective of the study in **chapter 5** was to demonstrate whether this effect on urodynamic parameters was visible after acute SNM. We demonstrated that there was no immediate effect of SNM on standard urodynamic parameters. In contrast, Dombek et al. recently demonstrated an acute effect of transcutaneous electrical nerve stimulation on urodynamic parameters in children with a neurogenic bladder.[33] The influence of the differences in age, bladder disorders, type of neuromodulation and underlying neurological disorder between Dombek et al. and our study **chapter 5**, is unclear. Apart from predicting success rates of SNM using urodynamic parameters, another argument to study acute effects of SNM is to explore the feasibility of a closed-loop feedback system, in which SNM is activated when the bladder pressure increases in the context of detrusor overactivity.[34,35] The effect of intermittent SNM seems comparable to that of continuous SNM, which might imply the appropriateness of such closed-loop feedback system.[36]

Predicting outcomes of therapies in patients with overactive bladder has not been very successful yet, causing that often multiple therapies are explored to find the most efficient one. **Chapter 5** is in accordance with other literature which mentions that objective parameters do not seem appropriate as prognostic measurements for the success of SNM treatment in overactive bladder.[29,30,37] The question raises whether dynamic brain imaging plays a future role as objective parameter in the prediction of responses to therapy. In this context, acute and chronic effects of SNM on activation patterns in brain areas have been demonstrated in patients.[38] For near future predictive models, the use of PROMS might be suitable, since the outcomes of objective and subjective measurements still seem to be very divergent in patients. The consistent use of validated PROMS

needs to be stimulated in order to increase the amount of high quality data towards such prediction model in functional urology.

Improvement of patient reported outcome measurements in functional urology

Physicians are trained proactively in including patients perspectives and to perform shared-decision making in order to maintain or improve quality of life (QoL) whilst improving survival. This has encouraged the development of PROMS. Important steps in implementation of questionnaires in health care are their translation and validation in the language and population in which they are used. In **chapter 6,** such translation and validation was executed, to make the "*OAB-q SF"* questionnaire usable in the Netherlands. For different diseases in functional urology, different PROMS have been translated and validated so far.[39-42] Health care organizations, such as the International Consortium for Health Outcome Measurements (ICHOM) have created 'core-sets' of questionnaires to use within a specific subspecialty or disease category and suggest worldwide consensus and use of these sets.[43] The use of these PROMS-sets has to be encouraged as a means to gather more data, which in turn would facilitate developing a good prediction model. This ICHOM initiative creates the possibility to compare results of therapy for different types of patients. The *OAB-q SF* questionnaire, is to be used in the work-up for patients with overactive bladder.[43] More knowledge on predicted outcomes might not only improve the success rates of conservative treatments but also achieve better patient selection for successful invasive treatments.

Improvement of patient selection for invasive treatments in functional urology

In the study presented in **chapter 7**, we investigated the outcomes of the construction of a continent catheterizable urinary channel in patients with bladder dysfunctions. In this invasive surgical procedure a urinary stoma is constructed on the anterior abdominal wall using a part of the bowel, and by catheterization of this stoma, the bladder can be emptied. The decision to undergo such invasive treatment with major impact on the patient's body image for a non-lethal disease is complex as the aim of the treatment is improvement of the QoL. The possible risks and benefits should therefore be weighted carefully.[44,45] A challenge in the decision making, is the lack of predictive factors for the risk of complications, and in case of complications a possible decrease in the QoL. Therefor the identification of these risk factors is important and could improve the patient selection for this treatment.[46,47] The study quality of **chapter 7** was limited, however, by the retrospective design. Since improvement in QoL is the aim of this therapy, this subjective outcome parameter should be reported pre- and postoperatively. Research in this patient category is hampered, by the limited number of patients, the heterogeneous disease presentation, and the differences between the various interventions

applied. A worldwide registry, with extensive and validated use of PROMS before and after surgery, including all patient characteristics, would possibly identify pre-operative risk factors for complications and might improve the patient selection for this treatment and other invasive treatments within functional urology. Within the near future, it might be optimistic to realize such registry. Therefore, until such implementation, all centers need to register PROMS and outcomes diligently to at least improve the quality of the available data.

EPILOGUE AND SUGGESTIONS FOR FUTURE RESEARCH

This thesis investigated the brain areas involved in central control of the LUT and thereby increased the knowledge on (patho-)physiology of bladder dysfunctions. Furthermore, with using 7T-fMRI we identified a possible objective outcome measurement within the field of functional urology. We have made progress in profound knowledge on both objective (urodynamic studies) and subjective (OAB-q SF questionnaire) outcomes measurements, and investigated the prognostic factors for complications on invasive surgery within functional urology. Functional urology is a challenging sub-specialty in which the use of a prudent combination of objective and subjective outcome measures is necessary to provide optimal care. There is room for improvement of these outcome measures, the possibilities of which we explored. However, still many questions remain. Therefore, suggestions for future research are divergent, ranging from basic science to postulate the pathophysiology of functional bladder disorders to clinical research yielding more data on outcome measures.

- In dynamic brain imaging, more individually assessable data needs to be generated on both healthy subjects and bladder dysfunction patients, with protocolled scan, task and analytic paradigms. This approach will increase the knowledge on the pathophysiology, and possibly reveal therapeutic targets.
- The search for alternative techniques to study activity patterns and therapeutic targets, that are easier accessible and less prone to artefacts needs to continue. Candidate techniques are near-infrared spectroscopy and transcranial magnetic stimulation.[48]
- In clinical practice, the use of standardized PROMS-sets needs to be encouraged, which will greatly contribute to developing of a good prediction model, thereby enlarging the chance of successful treatment in patients with functional bladder disorders.
- A registry needs to be developed for patients needing invasive treatments for functional bladder problems. This registry will, apart from the stimulation for the use of

PROMS before and after treatment, possibly identify risk factor for complications and therefor improve patient selection.

Without a long-term goal, we would have nothing to aim for: *What if we could combine the results of dynamic brain imaging with PROMS, in a future prediction model for functional bladder disorders including pain, which is realized by using a worldwide registry of patients with functional bladder disorders, therefore provide optimal personalized care, with high long-term success rates on therapies, and low chances on complications?*

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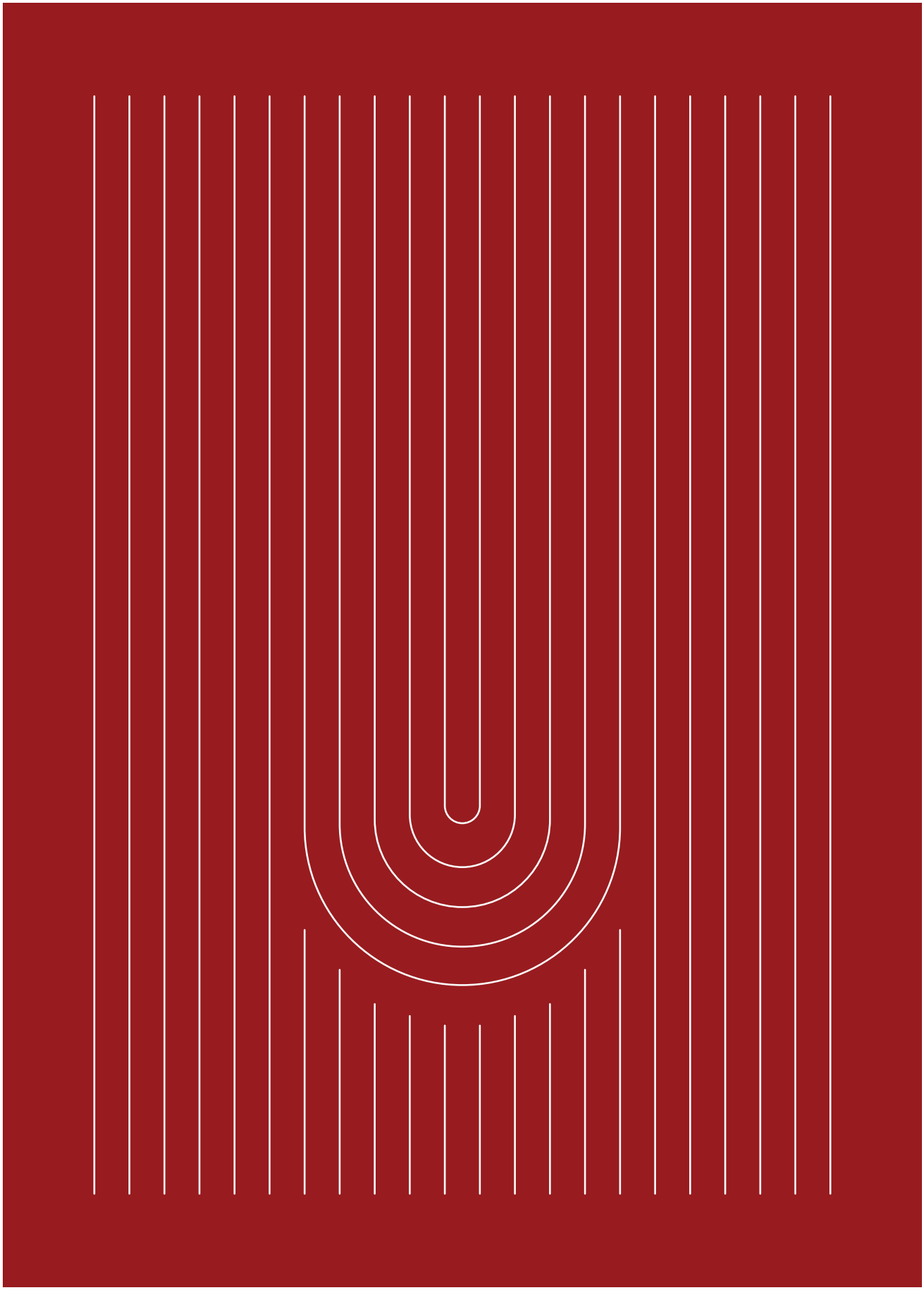


CHAPTER 9

Summary and Nederlandse samenvatting

SUMMARY

The field of functional urology includes functional disorders of the lower urinary tract (LUT), consisting of the bladder, its sphincters and the pelvic floor muscles. The physiology of the LUT with its peripheral and central innervation is explained in introductory **chapter 1** of this thesis. Furthermore, different disorders of the LUT with their symptoms and the diagnostics used are summarized. Relevant diagnostics include objective and subjective outcome measurements. Objective outcomes are measurements such as the number of voids per day or the post void residual. Subjective outcome measurements, usually in the form of a questionnaire, are designed to report patient's perceptions, such as the symptom bother and health-related quality of life. Additionally, in this chapter the working mechanism of dynamic brain imaging is explained, in particular the working mechanism of functional MRI (fMRI). Lastly, the available therapies for the subset of disorders are discussed, ranging from conservative, pharmacological to invasive treatments. It is emphasized, despite an increasing quality and amount of evidence in this field, there is a lack of knowledge on pathophysiology, diagnostics and therapies. This thesis aimed to investigate potential diagnostic tools in the field of functional urology and to improve objective and subjective outcome measurements.

The first part of this thesis reviews the present knowledge on brain control of the LUT and describes the usage of high-resolution 7T fMRI as a possible diagnostic tool in the field of functional urology. The brain areas involved in the innervation of the LUT were further defined, and we concluded that ultra-high field fMRI is a suitable technique to investigate brain areas involved in LUT control in individuals.

Chapter 2 describes a systematic review and meta-analysis which aimed to generate an overview of the brain areas involved in motor control of the LUT. Following a systematic search of the literature, 5718 publications were screened on relevance, of which in total 19 studies were included. Of these 19 studies, eleven investigated pelvic floor muscle contractions (PFMC) and eight micturition. All given coordinates of active clusters following the execution of these tasks were extracted by two authors independently. Using these coordinates, a coordinate-based meta-analysis was performed in the form of an activation likelihood estimation (ALE) analysis. ALE analysis uses the included coordinates as a spatial probability distribution to create a 'mean distribution'. To investigate PFMC, a total of 113 coordinates were entered, derived from 170 subjects. The results showed clusters in the primary motor cortex, supplementary motor areas, cingulate gyrus, frontal gyrus, thalamus, supramarginal gyrus and the cerebellum. In the micturition ALE analysis, we entered 98 coordinates of a total of 107 subjects. It revealed clusters in the pontine micturition center, periaqueductal grey, cingulate gyrus, frontal gyrus, insula and ventral pons. When comparing the results of PFMC to those of micturition, we found that these two motor tasks of the LUT are innervated by distinct brain

areas, only showing overlap in the mid cingulate gyrus and the left thalamus. An important consideration when interpreting the results of **chapter 2** is the limited amount of data available for the ALE analysis. Moreover, it shows that more data is necessary on this topic to learn more about the physiology and subsequently the pathophysiology of diseases including motor control of the LUT. In this thesis the ALE analysis is used for the first time to investigate PFMC and the knowledge involved brain areas for specific tasks is increased.

To improve and enlarge data available on this topic, next to chapter 2, **chapter 3** and **chapter 4** report on our findings of 7T fMRI studies, during motor tasks and sensory tasks. We used group and individual analysis to investigate the brain areas involved in these tasks. The main goal of these studies was to investigate the applicability of 7T fMRI to study individual activity patterns involved in LUT control in the whole brain. For 7T fMRI to be suitable as potential diagnostic tool, significant results need to be available in individual patients.

Both chapters included 17 subjects. Data of four subjects could not be used due to motion artefacts. In **chapter 3**, subjects performed PFMC and tongue movements in the 7T MRI scanner. The latter task was chosen as mid-line control task. In **chapter 4**, tactile stimulation of the penile shaft was studied, with tactile stimulation of the feet served as control task. Data of both studies revealed that single subject results in the whole brain, were complementary to group results. An important finding of **chapter 4** is the location of activation on the primary sensory cortex (S1) during tactile stimulation of the penile shaft. The study showed that the genitalia are represented in the hip region in S1 and not below the feet, as stated in earlier publications with group analysis in lower resolution MRI scanners.

The studies presented in the second part of this thesis aimed to investigate and improve both objective and subjective outcome measurements within functional urology.

When a patient with overactive bladder does not respond to conservative or pharmacological therapies, a minimally invasive therapy known as sacral neuromodulation (SNM) can be considered. Before the lead and neuromodulator are implanted, SNM first need to be tested in a test-phase. The study presented in **chapter 5** investigated whether urodynamic parameters show an acute effect on SNM in patients with overactive bladder (OAB). There was a threefold rationale for this study. First, to increase knowledge on the working mechanism of SNM; second, to evaluate whether urodynamic parameters could be used instead of or complementary to this test-phase; and third, to investigate the usefulness of a 'closed-loop feedback system' in which SNM automatically activates when the bladder pressure increases. We found no acute effect of SNM on urodynamic parameters. This observation suggests that SNM primarily works via sensory pathways and not directly via motor pathways. This does not rule out the possible effects of a closed-loop feedback system, as explained in the discussion of **chapter 5**.

In functional urology, results of objective outcomes can diverge much from the results of subjective outcomes in the same patient. Functional disorders can cause a wide range of symptoms, of which the influence on quality of life can differ per person. Therefore, apart from objective measurements like bladder diaries and urodynamic studies, patient reported outcome measurements (PROMS) are of utmost importance. A worldwide often used questionnaire for patients with overactive bladder symptoms is the *OAB-q SF* which is included in the value-base healthcare consortium ICHOM dataset on OAB. **Chapter 6** reports how this questionnaire was translated and validated in the Dutch language. It appeared to be a valid PROM which now be used in clinical practice in the Netherlands.

The protocolled use of PROMS in clinical practice is encouraged, as it may lead to better outcomes of personalized therapies. Prognostic factors for outcomes of both conservative and invasive therapies have not yet been identified. The outcomes of a continent catheterizable urinary channel in adults were evaluated in the study presented in **chapter 7**. This invasive therapy for patients with functional bladder problems is not often performed, and consequently little is known on the risk factors for complications. All patients who received such channel during the past 20 years in either the Erasmus University Medical Center or the University Medical Center Groningen were retrospectively included in this study. The underlying cause for bladder disorders was neurogenic in 26 out of the 41 patients included in this study. The probability of a surgical revision of the channel due to complications like stenosis or leakage was greater than 40%. Apart from a higher age during surgery, no significant risk factors were identified, which is presumably related to the small patient sample. A future perspective is the development of a worldwide registry for patients who undergo invasive surgery for functional bladder disorders, including both objective and subjective outcome measurements. This will possibly identify risk factors for invasive surgery. As the development of such registers will take time, until implementation, centers need to be encourage to use validated and standardized outcomes.

In **chapter 8**, the general discussion of this thesis, the possible applicability of dynamic brain imaging in functional urology, as well as the applicability of dynamic brain imaging in individuals is discussed. Some potential issues are that the technique is time consuming and prone to artefacts, and that 7T is still limitedly available and relatively expensive. Most of these issues are resolvable, however, when technique evolves in due time. The general discussion furthermore describes that clinical research in functional urology is challenging due to the lack of reproducible objective parameters. The main goal is a better prediction on outcome measures and risk factors in individual patients. This is a prerequisite for personalized medicine in functional urology. Relevant research ranging from basic science to PROMS in clinical practice must be encouraged in order to improve health care in the field of functional urology.

NEDERLANDSE SAMENVATTING

De functionele urologie houdt zich bezig met functie stoornissen van de lage urinewegen, zoals de blaas en de bekkenbodem. **Hoofdstuk 1** beschrijft de functie van de lage urinewegen met de daarbij behorende perifere en centrale neuronale innervatie. Verder worden de verschillende stoornissen met de daarmee gepaarde klachten samengevat. De diagnostiek bestaat uit objectieve en subjectieve meetinstrumenten. Objectieve meetinstrumenten meten feitelijke gegevens over het lichaam, zoals de plasfrequentie op een dag of het residu van urine in de blaas na het plassen. De subjectieve meetinstrumenten - vaak in de vorm van een vragenlijst - meten hoeveel last iemand heeft van deze objectieve gegevens en hoe dit de kwaliteit van leven beïnvloedt. De functionele MRI (fMRI) is een relatief nieuwe dynamische beeldvormende techniek waarmee activatie van hersengebieden in beeld gebracht kunnen worden. Het is dus voorstelbaar dat veranderingen in de functie van de lage urinewegen ook veranderingen in bepaalde hersengebieden teweeg brengen. Daardoor kan de fMRI als objectief diagnostisch meetinstrument fungeren. De behandeling van functiestoornissen van de lagere urinewegen bestaat primair uit conservatieve maatregelen en medicamenteuze therapieën. Als deze therapieën niet voldoende werken, kunnen minimaal invasieve therapieën worden toegepast zoals sacrale neuromodulatie of meer invasieve reconstructieve ingrepen zoals het aanleggen van een continent katheteriseerbaar urinestoma.

In de afgelopen twee decennia is er veel kennis over de innervatie van de urinewegen verworven en zijn er nieuwe behandelmethoden ontwikkeld. Desondanks zijn er nog grote hiaten in de kennis van de verschillende pathomechanismen en is de wetenschap nog niet goed in staat om de verschillende behandelvormen goed te evalueren. Dit proefschrift heeft als **doel** om nieuwe en reeds bestaande objectieve als subjectieve meetinstrumenten binnen de functionele urologie te evalueren en te optimaliseren.

Deel 1 van dit proefschrift gaat in op de vraag of hoge-resolutie functionele MRI (7T fMRI) gebruikt zou kunnen worden in de diagnostiek binnen de functionele urologie. We hebben onder andere onderzoek verricht naar de hersengebieden die zijn betrokken bij het aansturen van de lage urinewegen, en aangetoond dat 7T fMRI een bruikbare techniek is om deze hersengebieden te onderzoeken.

In **hoofdstuk 2** wordt een systematisch literatuur onderzoek beschreven, wat als doel had een overzicht te genereren van de hersengebieden die betrokken zijn bij de motorische taken van de lage urinewegen. Middels een gerichte zoekopdracht, werden er 19 relevante artikelen geïncludeerd, waarvan 11 artikelen de aansturing van de bekkenbodemspieren betrof, en 8 artikelen de aansturing van de mictie betrof. Met de data uit de geïncludeerde artikelen hebben we een meta-analyse uitgevoerd in de vorm van een Activation Likelihood Estimation (ALE). In een ALE analyse worden de coördinaten van de hersengebieden die gerapporteerd worden in de geïncludeerde artikelen gezien

als een soort ruimtelijke kansverdeling van activatie. Alle coördinaten uit de artikelen worden samengevoegd en vormen een 'gemiddeld' activatie patroon. De ALE resultaten van de bekkenbodemcontracties lieten activatie zien van de primaire motorische schors, de supplementaire motorische schors, de gyrus cinguli, de gyrus frontalis, de thalamus, de gyrus supramarginalis en het cerebellum. Verder liet de ALE analyse van de mictie betrokkenheid zien van het pontine mictie centrum, de periaquaductale grijs, de gyrus cinguli, de gyrus frontalis, de insula en de ventrale pons. Een vergelijking van beide analyses leverde een overlap van cluster op in slechts twee hersengebieden; de gyrus cinguli en de linker thalamus. Ondanks dat de bekkenbodemcontracties en de mictie beide motorische taken van de lage urinewegen zijn, is het aannemelijk dat ze door verschillende hersengebieden worden aangestuurd. Bij de interpretatie van de resultaten van de ALE analyse is het goed om de beperkte hoeveelheid data waarmee de analyse is uitgevoerd in acht te nemen. Deze schaarste aan data demonstreert de noodzaak voor meer onderzoek op dit gebied en daarmee ook meer kennis over de (patho)fysiologie van de lage urinewegen. **Hoofdstuk 2** laat, voor het eerst een ALE analyse zien over de motorische aansturing van de bekkenbodem en heeft daarmee mogelijk de basis hersengebieden betrokken bij deze motorische taak bevestigd.

In de **hoofdstukken 3 en 4** worden de resultaten van 2 onderzoeken met 7T fMRI beschreven, namelijk betreffende respectievelijk motorische taken en sensorische taken. In eerste instantie is er een groepsanalyse gedaan van de verkregen data om de hersengebieden betrokken bij de bekkenbodemcontracties en de sensoriek van het genitaal te bestuderen. Daarnaast werd er in beide studies onderzocht of 7T fMRI gebruikt zou kunnen worden om het activatiepatroon van het hele brein in individuen te interpreteren. Als we 7T fMRI in de kliniek willen gebruiken, is het van belang dat we de resultaten op individueel niveau kunnen bekijken.

Aan beide onderzoeken deden 17 vrijwilligers mee maar wegens bewegingsartefacten konden we uiteindelijk data van 13 personen analyseren. In **hoofdstuk 3** voerden de vrijwilligers bekkenbodemcontracties uit, en als controletaak bewogen ze de tong. Omdat tongbeweging net zoals bekkenbodemcontractie een motorische taak is in de middenlijn van het lichaam maar toch op een hele andere plek zit, konden de resultaten in het brein goed met elkaar worden vergeleken. In **hoofdstuk 4** werden de hersengebieden die betrokken zijn bij het gevoel van de penis onderzocht en hierbij werd de aanraking van de voeten gebruikt als controle. Om aan te tonen waar op de primair sensorische schors de penis is gerepresenteerd, kon activatie tijdens voet aanraking goed gebruikt worden als referentiepunt. Beide onderzoeken lieten zien dat 7T fMRI geschikt is om de betrokken hersengebieden van de lage urinewegen te bestuderen in het gehele brein van een individu. Dit in tegenstelling tot eerder gepubliceerd onderzoek waar veranderingen in hersenactivatie slecht na groepsanalysen werd getoond. Een belangrijke bevinding in **hoofdstuk 4** is de locatie van de activatie op de primaire sensorische

schors bij een tactiele stimulus van de penis. Het onderzoek toonde duidelijk aan dat de genitalia in de heup regio gerepresenteerd zijn op de primaire sensorische schors, en niet mediaal-craniaal van de plek op de primaire sensorische schors waar de voeten zijn gerepresenteerd, zoals eerder is vastgesteld.

Het tweede deel van dit proefschrift had als doel het evalueren en verbeteren van objectieve en subjectieve uitkomstmaten binnen de functionele urologie.

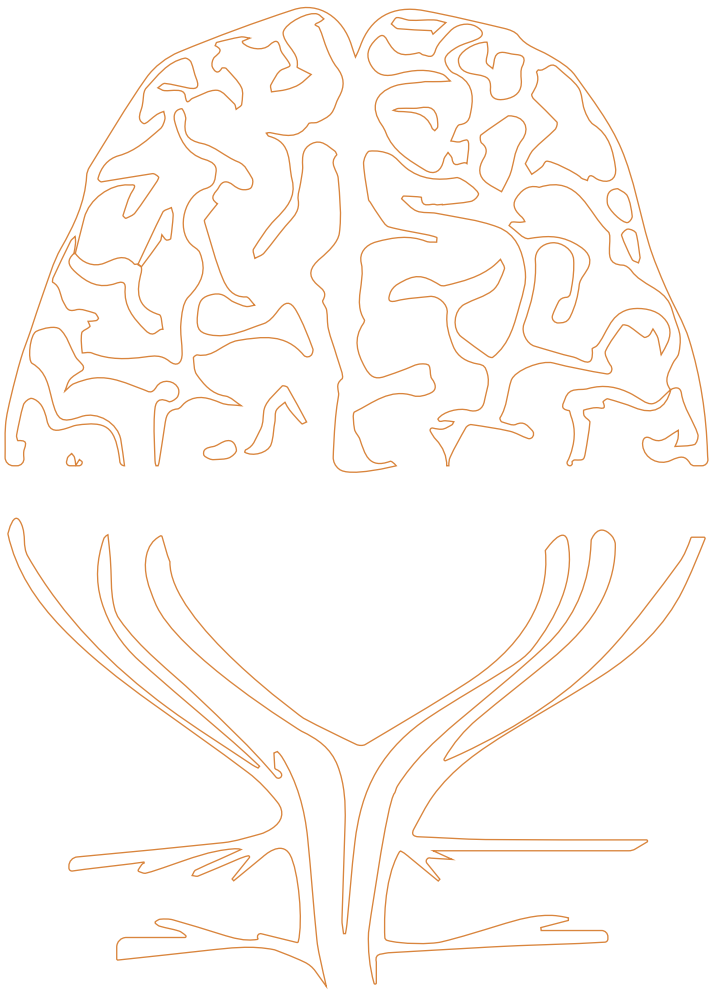
Als patiënten met overactieve blaas niet reageren op conservatieve of medicamenteuze therapieën, kan er gekozen worden om sacrale neuromodulatie toe te passen. Dit wordt gezien als een minimaal invasieve behandeling. Omdat op basis van de kenmerken van een patiënt nog niet goed voorspeld kan worden of diegene wel of geen baat heeft bij deze behandeling, wordt er eerst een test stimulatie uitgevoerd met een externe batterij als stimulator. Als blijkt dat er voldoende effect is, kan het definitieve systeem worden geïmplanteerd. In **hoofdstuk 5** is met behulp van urodynamisch onderzoek onderzocht of er een acuut effect op de blaas dynamiek te zien is van de sacrale neuromodulatie. Een acuut effect bleek niet op te treden. Een doel om het acute effect van sacrale neuromodulatie te onderzoeken is om na te gaan in hoe verre een 'closed-loop feedback systeem' met sacrale neuromodulatie werkzaam is. Met dit systeem wordt de neuromodulator automatisch geactiveerd als de druk in de blaas toeneemt. Ondanks het feit dat er geen acuut effect op het urodynamisch onderzoek meetbaar is sluiten deze resultaten een mogelijk closed loop systeem niet bij voorbaat uit. De theorie hierachter is dat het effect van sacrale neuromodulatie in het brein enige tijd blijft bestaan, nadat de sacrale neuromodulatie is gestopt. Met een 'closed-loop feedback systeem' zou deze 'verandering' in het brein onderhouden kunnen worden en dus het effect van de sacrale neuromodulatie weer kunnen oproepen. Meer onderzoek naar deze theorie is noodzakelijk om het systeem verder te ontwikkelen.

Binnen de functionele urologie komen de objectieve uitkomsten vaak niet overeen met de subjectieve parameters. De invloed van symptomen op de kwaliteit van leven verschilt sterk per individu. Daarom zijn naast de objectieve uitkomsten ook de subjectieve uitkomstmaten van groot belang. Een wereldwijd veel gebruikte subjectief meetinstrument is de vragenlijst *OAB-q SF* voor patiënten met overactieve blaas. In **hoofdstuk 6** is beschreven hoe deze vragenlijst in het Nederlands vertaald en gevalideerd werd. De Nederlandstalige versie bleek een valide meetinstrument voor de perceptie van de patiënt met overactieve blaasklachten.

Hoofdstuk 7 onderzoekt de uitkomsten van het aanleggen van een continent katheteriseerbaar urinestoma. Deze ingreep komt oorspronkelijk vanuit de kinderurologie maar wordt in uitzonderlijke gevallen ook bij volwassenen met therapieresistente blaasfunctiestoornissen gebruikt. Over de lange termijn resultaten en complicaties van deze ingreep bij volwassenen is nog weinig bekend. In een retrospectief onderzoek werden de gegevens van alle patiënten die in de afgelopen 20 jaar een dergelijke ingreep heb-

ben ondergaan geanalyseerd. In totaal werden 41 patiënten in deze studie geïncludeerd waarvan 26 met een neurogene oorzaak van de blaasfunctiestoornissen. De kans op een heroperatie wegens een stoma gerelateerd probleem was 40%. Er was geen verschil tussen de neurogene en niet-neurogene patiënten. Ook andere risicofactoren konden niet geïdentificeerd worden behalve een hoge leeftijd op het moment van de ingreep.

In **hoofdstuk 8**, de algemene discussie van dit proefschrift, wordt onder andere de mogelijk klinische toepassing van 7T fMRI besproken. Hoofdstukken 2, 3 en 4 dragen bij aan de kennis over de hersengebieden betrokken bij de lage urinewegen en hoofdstukken 3 en 4 tonen aan dat deze techniek ook op individueel niveau gebruikt kan worden binnen dit vakgebied. Enkele kanttekeningen moeten hierbij worden geplaatst. De analyse neemt veel tijd in beslag, de techniek is duur, gevoelig voor artefacten en vooralsnog beperkt beschikbaar. Na verdere ontwikkeling en verbetering kan de techniek daadwerkelijk in de praktijk worden gebruikt. Hoofdstukken 5, 6 en 7 dragen bij aan de verbetering van zowel de objectieve als de subjectieve uitkomstmaten. Een belangrijk doel binnen de functionele urologie is om de uitkomsten van therapie en de kans op complicaties of bijwerkingen beter te kunnen inschatten en hierdoor een passende behandeling per patiënt aan te kunnen bieden. Het onderzoek naar zowel objectieve als subjectieve uitkomsten beschreven in dit proefschrift draagt bij aan deze personalisatie van zorg binnen de functionele urologie.



PART IV

APPENDICES

Author Affiliations
List of Publications
Erasmus MC Portfolio
About the Author
Acknowledgments/Dankwoord

AUTHOR AFFILIATOINS

Bertil F.M. Blok	Erasmus Medical Center, Rotterdam, The Netherlands *Department of Urology*
Becky D. Clarkson	University of Pittsburgh, Pittsburgh, USA *Division of Geriatric Medicine*
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Chris I. de Zeeuw — Erasmus Medical Center, Rotterdam, The Netherlands
Department of Neuroscience
Netherlands Institute for Neuroscience, Amsterdam, The Netherlands

Wietske van der Zwaag — Spinoza Center for Neuroimaging, Amsterdam, The Netherlands

LIST OF PUBLICATIONS

Groenendijk IM*, Mehnert U*, Groen J, Clarckson BD, Scheepe JR, Blok BFM
A systematic review and activation likelihood estimation meta-analysis of the central innervation of the lower urinary tract: pelvic floor motor control and micturition
Submitted for publication

Coolen RL, Groenendijk IM, Blok BFM
Recent advances in neuroimaging of urinary bladder function, defecation and sexual function
Accepted for publication in Curr Opin Urol

Luijten SPR*, Groenendijk IM*, Holstege JC, de Zeeuw CI, van der Zwaag W, Blok BFM
Single subject and group whole-brain fMRI mapping of male genital sensation at 7 Tesla
Sci Rep. 2020 Feb 12;10(1):2487

Groenendijk IM, Scheepe JR, Blok BFM, Nijman RJM, van den Hoek J
Langetermijnresultaten van continent katheteriseerbare urostoma's bij volwassenen met niet-neurogene of neurogene blaasontledigingsstoornissen
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Int J Pediatr Otorhinolaryngol. 2016;84:161-5

Van der Valk JPM, van Wijk G, Hoorn E, Groenendijk L, Groenendijk IM, de Jong NW
Measurements and interpretation of skin prick test results
Clin Transl Allergy. 2016 Feb 23;6:8

Hartman EM*, Groenendijk IM*, Heuvelman HM, Roos-hesseling JW, Takkenberg JJ, Witsenburg MEMJ
The effectiveness of stenting of coarctation of the aorta: a systematic review
EuroIntervention. 2015;11(6):660–668

**Equal contribution*

PHD PORTFOLIO

Summary of PhD training and teaching

Name PhD student: Ilse Marie Groenendijk
Erasmus MC Department: Urology
Research School: MolMed

PhD period: 01-01-2017 – 31-12-2019
Promotor(s): prof. dr. C.H. Bangma
Supervisor: dr. B.F.M. Blok & dr. J.R. Scheepe

1. PhD training

	Year	ECTS
General courses		
- Research Integrity	2017	0.3
- CPO course	2017	0.3
- Biomedical English Writing Course	2017	2.0
- BROK 'Basiscursus Regelgeving Klinisch Onderzoek'	2017	1.5
- Endnote course	2017	0.3
- Basic Introduction Course on SPSS	2017	1.0
Specific courses		
- Trialmeeting: The Niagara EU investigator meeting, London, United kingdom.	2018	1.0
Seminars and workshops		
- Department Journal Club	2017 - 2019	3.0
- Educational program Urology (Refereeravonden EMC/LUMC/SFG/Amphia/HAGA)	2017 - 2019	1.0
- Educational evenings (RUAG)	2017 - 2019	1.0
Presentations		
- Oral case presentation 15 min at International Neuro-Urology Meeting, Zurich, Switzerland	2018	0.7
- Poster presentation at the 33rd Annual EAU congress Copenhagen, Denmark	2018	0.7
- Oral presentation at Sophia research day, Erasmus MC, Rotterdam	2018	0.7
- Poster presentation at the ICS meeting, Philadelphia, USA	2018	0.7
- Oral presentation "Refereeravond" at Erasmus MC, Rotterdam	2018	0.7
- Abstract presentation at the NVU najaarsvergadering, Nieuwegein	2018	0.7
- Abstract presentation at the symposium experimenteel onderzoek heelkundige specialismen, Rotterdam	2018	0.7
- Poster presentation at the Internation Neuro-Urology meeting, Zurich, Switzerland	2019	0.7
- Extended poster presentation at the 34th Annual EAU congress, Barcelona, Spain	2019	0.7
- Abstract presentation at the NVU voorjaarsvergadering, Rotterdam	2019	0.7

	Year	ECTS
(Inter)national conferences		
- 6th International Neuro-Urology Meeting, Zurich, Switzerland	2018	1.0
- 33rd Annual EAU congress, Copenhagen, Denmark	2018	1.0
- NVU voorjaarsvergadeing, Nieuwegein	2018	0.3
- Sophia research day, Rotterdam	2018	0.3
- ICS meeting, Philadelphia, USA	2018	1.0
- NVU najaarsvergadering, Nieuwegein	2018	0.3
- SEOHS (symposium experimenteel onderzoek heelkundige specialismen, Rotterdam	2018	0.3
- 7th international Neuro-Urology meeting, Zurich, Switzerland	2019	1.0
- 34th Annual EAU congress, Barcelona, Spain	2019	1.0
- NVU voorjaarsvergadering, Rotterdam	2019	0.3
Other		
- Bestuurslid, (penningmeester) bij RUAG, Rotterdams Urologisch Assistenten Genootschap	2017 - 2020	2.0
2. Teaching		
- VO lichamelijk onderzoek van de man, (6 times)	2017 - 2019	1.0
- IWK (interactief werk college) incontinentie, (5 times)	2018 - 2019	1.0
- Course on coaching bachelor students	2018	0.2
- Intervision on coaching	2018	0.2
- Talentinterview training in coaching	2018	0.2
- Coaching bachelor students, 2018-2019	2018 - 2020	2.0
Supervising interns		
- During clinical hours at the paediatric urology department	2017	1.0
Grants and prices		
- Erasmus MC Trustfonds congress participation grant, € 500,-, August 2018	2018	
Total		32.5

ABOUT THE AUTHOR

Ilse Marie Groenendijk was born on June 7th 1990 in the Dijkzigt Ziekenhuis in Rotterdam, the Netherlands. After graduating from secondary school in 2009 (Libanon Lyceum, Rotterdam), she started studying Medicine at the Erasmus University Rotterdam. Ilse's first research experience was at the Department of Cardiology during the second year of her medical study. After obtaining her bachelor's degree, Ilse performed her 6-months scientific internship under supervision of Prof. M. van Dijk at the Department of Pediatric Surgery, Red Cross War Memorial Children's Hospital, Cape Town, South Africa, and continued this research during her medical internships in Rotterdam. During these medical internships, Ilse developed a specific interest in Urology and was involved in scientific research in the field of Pediatric Urology under supervision of drs. K. Wolffenbuttel. In March 2016, Ilse obtained her medical degree and started to work as a resident (not in training) at the Department of Urology in the IJsselland Ziekenhuis, Capelle a/d IJssel. In 2017 she started her PhD at the Department of Urology, Erasmus MC, under supervision of Prof. dr. C.H. Bangma, dr. B.F.M. Blok and dr. J.R. Scheepe. During the first year, this position was in combination with working as a resident at the Department of Pediatric Urology, followed by two full-time years PhD study. Ilse will defend her thesis in the summer of 2020 at the Erasmus MC. From May 2020 Ilse will work as a resident in training at the Department of General Surgery, Maasstad Ziekenhuis under supervision of dr. R. Klaassen, as a part of her Urology traineeship. In 2022 Ilse will continue this traineeship at the department of Urology in the Erasmus MC, under supervision of dr. J.R. Scheepe.

DANKWOORD

Toen ik een aantal jaar geleden met familie en vrienden om me heen sprak over het doen van promotie onderzoek, kwamen er van meerder kanten dezelfde reacties: *Jij? Maar daar moet je toch 3 jaar voor op een stoel kunnen zitten?... en een hele tijd niks zeggen?* Nu is dit proefschrift om twee redenen daadwerkelijk tot stand gekomen. Dat is door mijzelf, maar zeker niet minder belangrijk, door de mensen om mij heen. Ik wil iedereen, die op welke manier dan ook betrokken is geweest in deze periode, ongelooflijk bedanken voor de steun, de aanmoediging en het geduld. Ik was bang dat dit het langste hoofdstuk van het proefschrift ging worden, en dat is bijna gelukt, dus ga er even lekker voor zitten ;).

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applausjes en rare fratsen. Jullie hebben een onvergetelijke rol gespeeld in deze periode en ik had me geen betere groep gekken kunnen wensen.

Functionele damessss Tess, Sophie en Rosa: veel succes met de voortzetting van onze onderzoeksgroep. Ik heb veel vertrouwen dat jullie het naar een volgend level gaat tillen met z'n drieën. Geloof in je talent en geef niet op!

Lieve Toscane, als maatjes gingen we er samen tegenaan en hebben we elkaar gesteund. Ik heb erg veel respect voor hoe jij je door het afgelopen jaar hebt heen geslagen en de desondanks grote glimlach die altijd op je gezicht verschijnt! Ik vind het super gezellig dat onze paden nog zo vaak gaan kruisen de aankomende 6 jaar.

Lieve Raya, zoals ik je laatst zei: Ik neem een voorbeeld aan jou gedrevenheid en passie voor het vak en hoop dat ik na m'n opleiding net zo'n goede dokter ben als jij.

Dames 4: hier spreekt jullie captain Pils op een (wederom) prachtige zondag: "Wat hebben we vandaag weer een IJZER-STERKE selectie, om gehakt te maken van …….(tegenpartij, helaas erg vaak afkomstig uit 020)". Er komt een nieuwe fase aan, waarin ik niet meer als kapitein van het schip zal fungeren. Ik heb er ongelooflijk van genoten! Bedankt voor de afleiding, Dames 4 4life, we love HK.

Bodine, Dokter B….. (vul de rest maar zelf in) in hetzelfde hockey team, allebei promotie in het Erasmus MC, en nu allebei in opleiding tot uroloog. Jij doet alles met 200% en staat tegelijk voor iedereen klaar. Ik heb heel veel respect voor je en ben super blij om zo veel met je te delen.

Lieve Malou, we werkte allebei hard om ons doel te bereiken. Maar waar mijn doel een paar maanden werd uitgesteld, is dat van jou een heel jaar uitgesteld. Gelukkig kan jij doorzetten als geen ander en ik weet zeker dat Tokyo wacht op een ster zoals jij!

Isabel, Iesje Piesje Pindasaus, je wilt niet weten hoe blij ik ben dat ik jou heb leren kennen. De hoeveelheid lol die ik met jou gehad heb de laatste jaren is bizar. Ondanks dat we concurrenten waren zijn we elkaar blijven steunen en aanmoedigen en is het ons samen gelukt. Heel erg bedankt voor alle gekte en plezier, en ik hoop dat we nog jaren zo door kunnen gaan.

Lieve Norah, mijn Nurdies, we werden vriendinnen toen we 5 jaar oud waren en al die jaren al steunen we elkaar door dik en dun. Wat ben ik dankbaar dat jij nog steeds mijn vriendin bent.

Mijn Lowlands vriendinnen Fenna, Loui, Marjo en Scar: Als je ons tekeer ziet gaat in Biddinghuizen gelooft natuurlijk niemand dat het gaat om een psychiater i.o., een dermatoloog i.o., een gynaecoloog i.o., een huisarts i.o., en een uroloog i.o. Wij zelf ook niet helemaal. Maar toch hebben we het geflikt! Ik ben super trots op ons en hoop dat we het heerlijkste uitje van het jaar als traditie in stand kunnen houden!

Lieve Marjo, mijn midget-marjo, mijn midgelien: onze drukke agenda's zijn een klein obstakel de laatste tijd, toch weten we onze mooie, bijzondere vriendschap in leven te houden omdat het gewoon zo fijn is om samen te zijn. Wij begrijpen elkaar zo goed! Bedankt voor je al je support.

De DOBO, bedankt voor de heerlijk afleiding en gekkigheid. We komen in een nieuwe fase terecht waarin de kroeg mogelijk (deels) verruild gaat worden voor de dierentuin, maar dat maakt het niet minder gezellig!

Lieve Died, mijn eeuwige buurman, tijdens alle koffies en biertjes kunnen we overal over praten en met name erg veel lachen. Je bent zo behulpzaam en staat echt altijd voor ons klaar. Bedankt daarvoor. Natuurlijk wil ook mijn echte bauermannen en bauervrouwen bedanken dat we altijd welkom zijn. Zo gezellig! En sorry dat we de kat soms inpikken ;)

Lieve Florine, in onze ruim 14 jaar vriendschap hebben we samen een hoop meegemaakt en voelt het alsof je m'n familie bent. Bedankt voor je oneindige interesse, attente kaartjes, berichtjes en belletjes.

Natuurlijk wil ik ook mijn lieve schoonfamilie Yvette, Richard en Josien, Sabine, Tiger, River, Alexander en Tamara bedanken voor hun interesse en alle fijne momenten in Spanje!

Lieve Opa en Oma, wat bijzonder dat ik dit proefschrift aan jullie kan laten zien. Opa, ik heb veel geleerd van onze gesprekken over het leven. We kunnen zo goed met elkaar praten. Je bent me ongelooflijk dierbaar en ik ben heel trots op je hoe je in deze fase van je leven de draad steeds weer oppakt. Lieve Oma, de hoeveelheid liefde die ik in m'n leven al van jou ontvangen hebt is ongekend. Ik had me geen lievere Oma kunnen wensen.

Lieve pap, jouw humor en eigenzinnige blik op het leven leren mij dat het niet alleen om prestaties of werk gaat, en daar ben ik je erg dankbaar voor. Wat is het heerlijk om samen naar muziek te luisteren en liefde aan elkaar te geven. Bedankt voor alle warmte die ik van je krijg, ik ben trots dat ik jou dochter ben. Lieve Margot, je bent een van de liefste

vrouwen die ooit heb ontmoet, wat ben ik blij dat ik jou familie mag noemen. Bedankt voor AL het lekker eten en de gezelligheid!

Lieve mam, als er één iemand is aan wie ik dit proefschrift te danken heb, dan ben jij het. Je bent mijn grote voorbeeld en hebt mij laten zien dat alles mogelijk is in dit leven als je er maar voor gaat. Hoe ontzettend zorgzaam en lief jij kan zijn voor zo veel mensen tegelijk is voor mij een raadsel. Je hebt me door alle scholen en opleidingen aan de hand meegenomen, altijd in me geloofd, me aangemoedigd en me geholpen. Er zijn geen woorden te vinden die omschrijven hoe dankbaar ik je daarvoor ben. Lieve Folkert, wat fijn dat mama bij jou rust en liefde krijgt. Je bent een rots in de branding.

Lieve Loes, je bent gewoon serieus de aller leukste zus die ik me ooit had kunnen wensen. Onze band is zo sterk dat we soms als 1 aanvoelen. Je bent m'n aller beste vriendin en soul-mate en ik ben ongelooflijk trots dat je vandaag naast me staat als m'n 'paradinges'. Dat je deze zomer moeder wordt, zal voor ons allemaal iets heel bijzonders zijn en ik kan echt niet wachten om mijn nichtje te ontmoeten. Ben is een super liefdevolle aanvulling in jou leven en ik gun jullie al het geluk op deze wereld.

Lieve Diek, toen jij mij (na enig aandringen) in 3 havo verkering vroeg had ik natuurlijk nooit gedacht dat jij 14 jaar later nog steeds de hoofdpersoon in mijn leven zou zijn. En na al die jaren kan ik soms nog steeds niet geloven dat jij echt bestaat. Terwijl je me in balans houdt steun je me in alles wat ik doe en daar ben ik je eindeloos dankbaar voor. Het maakt niet zo veel uit waar op deze planeet we zijn, want als we samen zijn, zijn we thuis en ik geloof dat dat voor altijd zo gaat blijven.