The influence of sacral neuromodulation on brain areas involved in the sensation of bladder filling in patients with Overactive Bladder (OAB) using fMRI

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2.1 Primary Objectives• To identify brain activation evoked by sensation in response to bladder filling in patients with an implanted sacral neurostimulator as a treatment for overactive bladder (OAB), compared to a baseline in OAB patients without…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Urinary tract signs and symptoms
Study type	Observational non invasive

Summary

ID

NL-OMON56105

Source
ToetsingOnline

Brief title
fMRI study of the influence of sacral neuromodulation on brain activity

Condition

- Urinary tract signs and symptoms

Synonym
Overactive Bladder Syndrome (OAB) / Overactive Bladder

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht

Source(s) of monetary or material Support: Ministerie van OC&W,Humane Meetmodellen 2.0

Intervention

Keyword: functional MRI, Overactive bladder, Sacral Neuromodulation, Urodynamics

Outcome measures

Primary outcome

We measure BOLD signal intensity changes in a priori supraspinal regions of interest (ROI), for example, periaqueductal grey, pons, insula, anterior cingulate cortex, thalamus, hypothalamus, supplementary motor area and prefrontal cortex, during fMRI in relation to the specific conditions, that is, low versus full bladder volume. The subjects register their bladder sensation during the fMRI scan. This is performed during tthree visits, once at baseline, once during testing phase of sacral neuromodulation (short-term) and once 3 months after implantation of a sacral neurostimulator (long-term). This will hopefully provide us with a better understanding of the working mechanism of sacral neuromodulation, which could lead to better assessment of patients that might be eligible for treatment with sacral neuromodulation.

Secondary outcome

- The fMRI is made at two timepoints during the treatment: 2-5 days after implanting the neurostimulator, and 3 months later, comparing the difference between short-term and long-term activation patterns of the brain during sacral neuromodulation, and comparing results with healthy participants without OAB.
- A comparison will be made between responders and non-responders, looking at possible structural differences in brain activation during the pre-implantation

phase, and comparing results with healthy participants without OAB. This could contribute to the assessment of patients that have an indication for treatment with sacral neuromodulation.

- The extent of bladder filling and bladder sensations will be compared before and after implantation of the neurostimulator, correlating it to changes in brain activation, and comparing results with healthy participants without OAB.

Study description

Background summary

Patients that are diagnosed with overactive bladder syndrome (OAB), are eligible for treatment with sacral neuromodulation after failing other therapies such as physio- and behavioural therapy, medication or intravesical botulinum toxin injections. Despite the fact that sacral neuromodulation is an approved and widely used therapy since the 1990*s, the exact working mechanism of sacral neuromodulation, and its specific effect on brain activation during bladder filling and urgency are not clear yet. Because this working mechanism is still largely unknown, we are unable to understand what causes the success of a treatment, and predict which patients will respond positively to the therapy. For this reason, a two-step implantation is performed. This allows us to test the system first, and see if that particular patient responds well to the therapy, before implanting the total system.

The effect of sacral neurstimulation on brain activity during bladder filling has been studied few times, using fMRI or PET CT scans. These studies show that sacral neurostimulation therapy causes altered brain activation compared to a state before sacral neurostimulation. However, these results are not unambiguously, and do not yet present a clear answer to the question. More studies need to be executed, in order to really understand the working mechanism of sacral neuromodulation.
This study will explore the influence of sacral neurostimulation on brain activation during bladder filling, gaining a better understanding of the working mechanism of this approved and widely used treatment. By using the ultra-high field 7T fMRI scanner, brain stem nuclei can be studied with unprecedented detail. Activity patterns within the periaqueductal gray (PAG) and the relation of the PAG to other brain regions that are associated with micturition and continence will be studied. Because this is the first time the brain activity in this population is studied in such detail, this research is

valuable and new in comparison to earlier studies. Moreover, this study will be an addition to a current study that is performed in our centre, looking at the difference in brain activity during bladder filling in women with and without OAB. These two studies can complement each other, and create the opportunity to gain even more knowledge about the pathology and treatment options in this patient group.
The ultimate aim is to allow a better patient selection in the future and this may ideally lead to the ability to perform a one stage procedure in eligible patients, which will reduce treatment cost, burden and complication risk for the patients.

Study objective

2.1 Primary Objectives
• To identify brain activation evoked by sensation in response to bladder filling in patients with an implanted sacral neurostimulator as a treatment for overactive bladder (OAB), compared to a baseline in OAB patients without treatment, conducted in another study, through fMRI during associated bladder sensation measurements.

2.2 Secondary Objectives
• To assess the difference in brain activity during bladder filling after short-term and long-term treatment with sacral neuromodulation, and comparing results with healthy participants without OAB.
• To assess the subjects bladder sensations measured by visual analogue scale (VAS) and 4-points grading scale (see Appendix 2) during natural bladder filling in fMRI scan, comparing before and after implantation, and comparing results with healthy participants without OAB.
• To assess the correlation between bladder filling and subject*s bladder sensations, comparing before and after implantation, and comparing results with healthy participants without OAB.
• To assess symptom severity, symptom bother and quality of life using: ICIQ-OAB, ICIQ-OABqol and a 3-day micturition bladder diary as background information to determine the difference before and after implantation, and comparing results with healthy participants without OAB.
• To assess the anxiety and depression status of study subjects through HADS questionnaire, comparing before and after implantation, and comparing results with healthy participants without OAB.
• To assess the severity and bother of sexual complaints, associated with OAB by using ICIQ-FLUTSsex, comparing before and after implantation, and comparing results with healthy participants without OAB.

Study design

All OAB patients will receive sacral neuromodulation as an intended treatment for their OAB symptoms. The study aims to identify brain regions involved in

the sensation of bladder filling that are influenced by sacral neuromodulation, using conventional urodynamic assessment in combination with bladder sensation assessment.
The study will be conducted according to open, uncontrolled, pretest-posttest group design.
Patients will be recruited via the urological outpatient clinic of the MUMC+ and Erasmus MC. They receive information about the study from a urologist or the nurse who provides neuromodulation care and who registers the patients for the procedure. A member of the research team will then contact the candidate to further explain the study or resolve any doubts, and give the candidate at least one week of consideration time. Afther this, the researcher contacts the candidate again, giving the candidate the opportunity to ask additional questions. If the patient agrees to participate, a screening visit will be set at the University/Urology Department with the researcher. At the start of this visit, the participant is able to ask any questions, and if they agree to participate, the informed consent will be signed. No study related procedures will take place before this step. After this screening appointment, the study will start, if the patient can be included. The subjects will receive maximally 4 extra visits compared to the regular treatment (1 screening visit, 2 or 3 separate scan sessions).
Healthy participants will be recruited through flyers and advertisements. The research team will also provide study information to interested participants via phone and e-mail after which they will also receive at least one week consideration time before a screening visit is planned.

As is standard treatment, the implantation of the sacral neuromodulation system will be performed in two steps. This 2 step procedure including a 2 weeks test stimulation is necessary as it is not known yet which patients will have a beneficial response to therapy, and which will not. A beneficial respons is defined as more than 50% improvement on one of the urinary complaints (urgency, frequency, voided volume and urinary loss), measured by a 3 day voiding diary filled out before and during testphase. During the first surgical procedure, the lead is implanted in foramen S3 (or in some cases S4), and is connected to an external testing device. When the patient has a beneficial respons to the therapy, during a second surgery, the lead will be connected to an internal pulse generator (IPG). This IPG is implanted in the gluteus maximus. In case the patient has little or no effect of the therapy, the testing system will be explanted during the second surgery.

The study participants will consist out of two groups defined as: Healthy individuals without OAB and not undergoing any treatments, and OAB subjects with or without detrusor overactivity (DO), that are eligible for treatment with sacral neuromodulation.
All healthy volunteers will complete the same procedures and assessments in the same order.
All patients that have a beneficial respons to sacral neuromodulation therapy will undergo a total of two 7 Tesla fMRI scans and pariticpants in Maastricht

will also complete a long-term follow up at 3T MRI scan at Scannexus in Maastricht, during all these scanning sessions their bladder is filled via natural diuresis and the subjects perform a task regarding their subjective bladder filling (IUSS and VAS score). For the patients that do not have a beneficial respons to the therapy, only two scans will be executed in the MUMC+ as well (baseline and during testing phase), and they will exit the study after explantation of the testing system for sacral neurmodulation.

Course of the study:
After the start of the study, an SR-BD (sensation related bladder diary) and questionnaires are completed (regular care), after which a baseline fMRI scan is performed (study - all study participants). Then the test phase of sacral neuromodulation is implanted in the operating room (regular care). 2-5 days after this the 2nd fMRI scan is performed (study - OAB group). The patient then completes an SR-BD and the questionnaires during the testing phase (regular care), and based on the results, receives an explantation of the testing system or an implantation of the IPG (regular care). The patient then completes an SR-BD and questionnaires again 3 months after implantation (study - MUMC+ only), and the last fMRI scan is performed (study - MUMC+ only).
After the last fMRI session, or after removing the test phase in case of insufficient effect, all data is collected and participation in the study is complete.

Study burden and risks

Most of the assessments performed during the study (physical examination, diary and questionnaires) are all part of the standard care for patients that are eligible for neuromodulation and they do not pose additional risk to patients. The pregnancy test is an extra test during this study, but does not pose an additional risk to the patients either. How to fill in these questionnaires and the diary will be explained to the patients carefully. We will focus on the fact that they have to complete the diary after every micturition, to keep the results as accurate as possible. The possible physical burden of the fMRI scan is explained in the next paragraph. A urodynamic investigation is part of the regular work-up for neuromodulation. The procedure will be explained carefully and the possible risks as well.
For the individual subjects there will be no additional personal benefit, but it will be explained that they are helping in improving the understanding of and possible future treatment for OAB. The time invested is explained in the participants* information letter. The fMRI is a new concept for most of the participants and is explained further below.

fMRI
1.5T and 3T MRI scanners are widely used in clinical environments. A static magnetic field of up to 14T or more does not harm biological tissue, but the radiofrequency and MR gradient applied can influence the human body via heating

(specific absorption rate (SAR)) or peripheral stimulation. Therefore, limits of the radiofrequency (RF) and magnetic resonance (MR) gradient are encoded in the MRI scanner. Certified users will always stay below these limits making scanning harmless. When scanning the subjects in this study, it is assured that the MRI field specifications that are stated in the product brochures of the sacrale neuromodulation system are not exceeded. Other metallic objects however cannot be inserted into the scanner area of the MRI scanner. Therefore, subjects with not-adequately fixed metallic prostheses, non MRI safe pacemakers, metal clips on blood vessels, metal parts in the eye, an intrauterine device (except for Mirena, a hormonal IUD), metal braces and other metal objects will be excluded from the study. Prior to scanning all subjects will fill out a form to screen for these metallic objects. Although 7T MRI is harmless if contra-indications are taken heed of and if operated by certified users, a small amount of people (5%) may experience vertigo or nausea while entering the scanner. However, slowing the subject*s entry and exit time into the magnetic field will minimize these symptoms. Also, a smaller amount of people may experience a metallic taste in their mouth during the scan.
The sacral neuromodulation system in this particular version has not been used during a 7 Tesla fMRI scan before. To predict the effect when patients with this device are placed in the fMRI scan, a safety analysis has been performed. This analysis shows no significant side effects to be expected during the study.

There is no intended direct clinical benefit for the subjects participating to this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. Female subjects above 18 years of age.
2. Has provided written informed consent prior to any study related procedures.
3. Indication for treatment with sacral neuromodulation (for patient group)
4. History of signs and symptoms of OAB including urinary frequency, urgency or urge incontinence for greater than or equal to 3 months. (for patient group)
5. The subjects must have (for patient group):
a. At least 1 episode of urgency with or without incontinence in the last 3-day micturition diary.
b. Frequency of micturition greater than or equal to 8 per 24 hours period during the 3-day micturition diary period
6. At the screening visit, when patient is on medicinal treatment for OAB they should be willing to undergo a washout period for 3 weeks. (for patient group)

Exclusion criteria

1. Stress urinary incontinence more profound than urge urinary incontinence, urethral sphincter incompetence and neurogenic detrusor overactivity.
2. Current urinary tract infection (confirmed by positive urine analysis).
3. Bladder outlet obstruction (not including detrusor-overactivity), for example bladder/vesico-uterine prolapse (> grade II) or chronic obstruction.
4. History of urinary tract surgery less than or equal to 6 months prior to screening.
5. Intermittent catheterization or permanent catheter.
6. History of pelvic area radiotherapy treatment.

7. Has a history of treatment of OAB with botulinum toxin within less than 12 months prior to screening.
8. Patients with any metal implants in the body (except dental implants) that would prevent the patients to undergo fMRI scan, excluding MRI safe nerve stimulators.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-01-2024
Enrollment:	95
Type:	Actual

Ethics review

Approved WMO Date:	13-07-2022
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	02-10-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL80374.068.22