Deep brain stimulation effects on lower urinary tract function: Systematic review and meta-analysis

Jörg, Elisa ; Sartori, Andrea M ; Hofer, Anna-Sophie ; Baumann, Christian R ; Kessler, Thomas M

Abstract: INTRODUCTION: While efficacy of deep brain stimulation for motor symptoms of neurological disorders is well accepted, its effects on the autonomic system remain controversial. We aimed to systematically assess all available evidence of deep brain stimulation effects on lower urinary tract function. METHODS: This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Studies were identified by electronic search of Cochrane Central Register of Controlled Trials, Embase, Medline, Scopus, and Web of Science (last search July 12, 2019) and by screening of reference lists and reviews. RESULTS: After screening 577 articles, we included 29 studies enrolling a total of 1293 patients. Deep brain stimulation of the globus pallidus internus (GPi), pedunculopontine nucleus (PPN), and subthalamic nucleus (STN) had an inhibitory effect on detrusor function, while deep brain stimulation of the ventral intermediate nucleus of the thalamus (VIM) showed an excitatory effect. In the meta-analysis, deep brain stimulation of the STN led to a significant increase in maximum bladder capacity (mean difference 124 mL, 95% confidence interval 60-187 mL, p = 0.0001) but had no clinically relevant effects on other urodynamic parameters. Adverse events (reported in thirteen studies) were most commonly respiratory issues, postural instability, and dysphagia. Risk of bias and confounding was relatively low. CONCLUSIONS: Deep brain stimulation does not impair lower urinary tract function and might even have beneficial effects. This needs to be considered in the deep brain stimulation decision-making process helping to encourage and to reassure prospective patients.

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Review article

Deep brain stimulation effects on lower urinary tract function: Systematic review and meta-analysis

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ABSTRACT

Introduction: While efficacy of deep brain stimulation for motor symptoms of neurological disorders is well accepted, its effects on the autonomic system remain controversial. We aimed to systematically assess all available evidence of deep brain stimulation effects on lower urinary tract function.
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Results: After screening 577 articles, we included 29 studies enrolling a total of 1293 patients. Deep brain stimulation of the globus pallidus internus (GPi), pedunculopontine nucleus (PPN), and subthalamic nucleus (STN) had an inhibitory effect on detrusor function, while deep brain stimulation of the ventral intermediate nucleus of the thalamus (VIM) showed an excitatory effect. In the meta-analysis, deep brain stimulation of the STN led to a significant increase in maximum bladder capacity (mean difference 124 mL, 95% confidence interval 60–187 mL, $p = 0.0001$) but had no clinically relevant effects on other urodynamic parameters. Adverse events (reported in thirteen studies) were most commonly respiratory issues, postural instability, and dysphagia. Risk of bias and confounding was relatively low.
Conclusions: Deep brain stimulation does not impair lower urinary tract function and might even have beneficial effects. This needs to be considered in the deep brain stimulation decision-making process helping to encourage and to reassure prospective patients.

1. Introduction

Neurogenic lower urinary tract dysfunction (NLUTD) is highly prevalent in patients suffering from neurological disorders, and it may cause storage and/or voiding symptoms [1–3]. Patient's quality of life is frequently affected by NLUTD becoming one of the most challenging issues in the neurological patient [4]. Despite that, only few symptomatic treatments are currently available, including antimuscarinics, beta-3-adrenoceptor agonists, intradetrusor onabotulinumtoxinA injections, alpha-adrenoceptor blockers, indwelling/intermittent catheterization, neuromodulative and surgical procedures [4].

Deep brain stimulation (DBS) is a well-established and widely used surgical therapy for the treatment of the most common movement disorders, such as Parkinson's disease [5] and essential tremor [6]. DBS consists of the placement of leads in deep brain structures, i.e. different basal ganglia and brainstem nuclei and related tracts. DBS locally modulates the firing patterns of areas that are dysfunctional due to the ongoing pathology. Despite the widespread use of DBS, its precise mechanism of action remains enigmatic [7].

Although the main focus of DBS resides in the treatment of motor-associated symptoms in neurological patients [7,8], recent studies have suggested that patients suffering from non-motor symptoms, which

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strongly reduce the patients' quality of life, might also be beneficially influenced by this therapy [9,10]. While the efficacy of DBS for motor and selected non-motor (e.g. pain, sleep) symptoms is well accepted, its effects on the autonomic system are still controversial.

We therefore performed a systematic review and meta-analysis to assess, appraise, and analyze all available evidence of the effects of DBS on lower urinary tract function.

2. Methods

2.1. Data sources and searches

The present systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [11]. The protocol for the review is available on PROSPERO (CRD42017064193) (http://www.crd.york.ac.uk/PROSPERO). We systematically searched Cochrane Central Register of Controlled Trials, Embase, Medline, Scopus, and Web of Science (from January 1, 1987 to July 12, 2019). No language restrictions were applied. We additionally searched the reference list of all included studies and any relevant review articles. An example of a MEDLINE search strategy is provided in Supplement 1.

2.2. Study selection

We aimed to include all original studies that reported data on the effects of DBS on lower urinary tract function including randomized controlled trials (RCTs), comparative non-RCTs, single-arm cohort studies, and case reports. Non-original articles and studies not published as full text were excluded. All identified abstracts were imported into a bibliography management software (EndNote X8; Thomson Reuters, Philadelphia, PA, USA) and sorted according to inclusion and exclusion folders by drag and drop. Abstracts of all identified studies were independently reviewed by two authors (EJ and AMS), and conflicts were resolved by a third reviewer (TMK). Studies reporting on the effects of DBS (defined as any electrical stimulation of deep brain structures) on lower urinary tract function were reviewed in full text.

2.3. Data extraction and risk of bias assessment

The variables assessed included: year of publication, study type, number of patients, gender and age, underlying neurological disorder, duration of neurological disorder, stimulation site, stimulation type (i.e. unilateral vs. bilateral), stimulation frequencies, pulse width, stimulation amplitude, DBS effects on urodynamic parameters (first desire to void, strong desire to void, maximum bladder capacity, maximum detrusor pressure, detrusor pressure during maximum flow rate, average flow rate, maximum flow rate, and post-void residual), and any adverse events. Data from eligible reports were extracted (by treatment group in comparative studies) in duplicate (EJ and AMS), and discrepancies were resolved by a third reviewer (TMK).

Non-comparative external validity was addressed by assessing whether study participants were selected consecutively or were representative of a wider patient population and whether specified confounding factors were reported and taken into account for analysis. The potential confounding factors are underlying neurological disorders (e.g. Parkinson's disease (PD), essential tremor, dystonia etc.), gender, age, site of stimulation, and stimulation parameters. Attrition bias and selective outcome reporting were also assessed (Supplement 2). This is a pragmatic approach informed by the methodological literature [12]. Finally, conflict of interest declarations, reporting of funding sources and role of any funding sources were investigated.

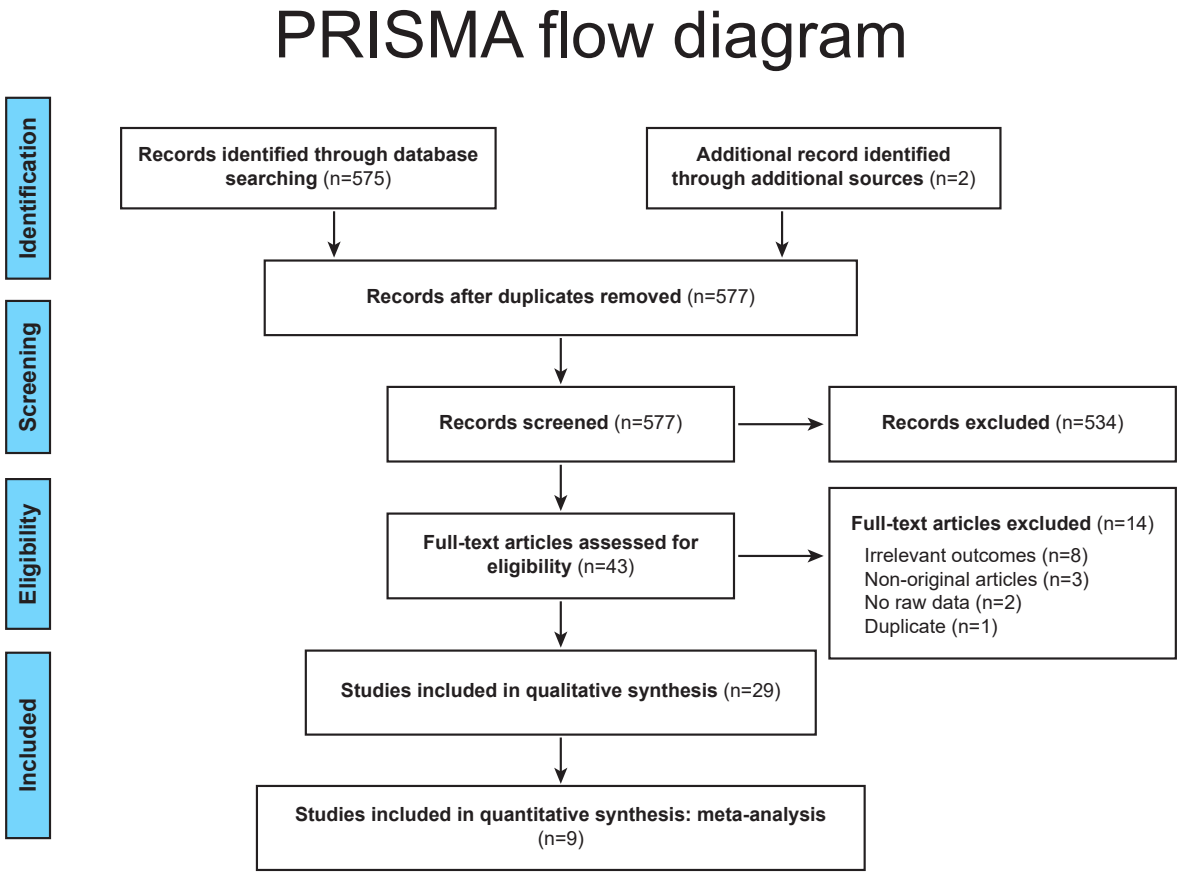


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram.

Table 1
Characteristics of included studies.

Type of study	Reference	Year of publication	Total patients [female/male]	Mean age [years]	Neurological disorder	Mean duration of neurological disorder [years]	Site of stimulation	Mean stimulation frequencies [Hertz]	Mean pulse width [μs]	Mean stimulation amplitude [volt]	Adverse events	Outcome measures
Case report	Aviles-Olmos [40]	2011	1 [0/1]	71	PD	20	PPN	30	60	3	Yes	AEs
	Liu [41]	2019	1 [1/0]	47	PD	20	GPi	80	130	3.1–3.3	Yes	AEs
Retrospective studies	Buhmann [38]	2017	123 [56/67]	59	PD [n = 82]; ET [n = 14]; dystonia [n = 18]; other [n = 9]	NR	STN; VIM; GPi	NR	NR	NR	Yes	AEs
	Nazzaro [39]	2011	24 [8/16]	64	PD	10.6	STN	NR	NR	NR	Yes	AEs; NMSQ; PDQ-39
Prospective studies	Dafsari [14]	2016	60 [25/35]	62	PD	10.5	STN	128	62.4	2.27–2.46	No	NMSQ; NMSS; PDQ-8
	Dafsari [15]	2018	67 [17/50]	62	PD	10.9	STN	128	62.4	2.27–2.46	No	NMSQ; NMSS; PDQ-8
	Dafsari [16]	2018	88 [32/56]	61	PD	10.5	STN	128	62.4	2.27–2.46	NR	NMSQ; NMSS; PDQ-8
	Dafsari [17]	2019	101 [36/65]	62	PD	10.7	STN	NR	NR	NR	Yes	NMSS; PDQ-8, AEs
	Finazzi-Agrò [18]	2003	5 [2/3]	63	PD	15	STN	185	90	1.5–2.5	Yes	AEs; BC; DCA; DCT; DPMF; MF
	Halim [19]	2011	3 [1/2]	52	PD	12.7	STN	NR	NR	NR	No	BD
	Herzog [20]	2006	11 [6/5]	58	PD	15.2	STN	143.6	61.4	3.3	Yes	AEs; FDV; SDV
	Herzog [21]	2008	9 [4/5]	60	PD	12.9	STN	157.8	60	3.4	No	FDV; SDV
	Hwynn [22]	2011	10 [NR]	66	PD	9.9	STN [n = 9]; GPi [n = 1]	NR	NR	NR	No	NMSQ; NMSS
	Kessler [23]	2008	7 [2/5]	66	ET	1.3–7.1	VIM	NR	NR	NR	No	BC; Compl.; DPMF; FDV; IPSS; MDP; MF; PVR; SDV; VV
	Merola [24]	2011	19 [10/9]	62	PD	23.9	STN	130	60	3	Yes	AEs
	Mock [9]	2016	20 [5/15]	61	PD	7.7	STN	NR	NR	NR	Yes	AEs; AUA-SI; OAB-q;
			13 [4/9]	64	PD	8	GPi	NR	NR	NR	Yes	PGI-I; QoL; SHIM
												AEs; AUA-SI; OAB-q; PGI-I; QoL; SHIM
	Mordasini [25]	2014	11 [5/6]	48	Dystonia	NR	GPi	NR	NR	NR	Yes	AEs; BC; DC; DPMF; FDV; IPSS; MDP; MF; PVR; SDV; VV
	Nakamura [26]	2019	21 [NR]	65	PD	12.2	STN [n = 18], GPi [n = 3]	NR	NR	NR	NR	Continence; PDQ-39
	Pietraszko [27]	2013	19 [4/15]	59	PD	11.9	STN	130	60	1–2	No	Frequency; hesitancy; nocturia; urgency [0–5 scale]
	Roy [28]	2018	5 [0/5]	63	PD	22.4	PPN	31	66	2.7	No	BC; FDV
	Rukmini	2015	56 [18/38]	57	PD	9.6	STN	NR	NR	NR	Yes	AEs; NMSQ
	Mridula [29]		53 [10/43]	57	PD	9.2	NA	NA	NA	NA	Yes	AEs; NMSQ
	Seif [30]	2004	16 [9/7]	62	PD	15	STN	NR	NR	NR	No	BC; DC; FDV; MDP; MF; PVR
	Shimizu [31]	2007	6 [2/4]	66	PD	NR	STN	130–185	60–120	0.5–2.6	No	BC; DPMF; DCT; IPSS; MF; PVR
	Winge [32]	2012	60 [29/31]	67	PD	10.5	STN	NR	NR	NR	Yes	AEs, DanPSS; IPSS
			38 [18/20]	60	PD	15.5	STN	NR	NR	NR		
	Witte [33]	2017	65 [21/44]	59	PD	10.8	GPi	137.5	73	2.9	Yes	AEs; Incontinence
			63 [19/44]	61	PD	12	STN	135	63.9	2.6	Yes	
	Wolz [34]	2012	34 [11/23]	68	PD	15.2	STN	NR	NR	NR	No	Urgency
	Yamamoto [35]	2018	28 [NR]	65	PD	11.8	STN [n = 22], GPi [n = 6]	NR	NR	NR	NR	

(*continued on next page*)

Table 1 (*continued*)

Type of study	Reference	Year of publication	Total patients [female/male]	Mean age [years]	Neurological disorder	Mean duration of neurological disorder [years]	Site of stimulation	Mean stimulation frequencies [Hertz]	Mean pulse width [μs]	Mean stimulation amplitude [volt]	Adverse events	Outcome measures
												AF; DO; FDV; IPSS; MF; OABSS; PVR; SDV
	Zibetti [36]	2007	36 [14/22]	61	PD	16.7	STN	136	65	3.3	No	BD
	Zong [37]	2019	220 [60/160]	61	PD	7.7	STN	NR	NR	NR	No	AUA-SI; BC; Compl.; DPMF; FDV; MF; OABSS; PVR; QoL;

AEs = adverse events; AF = average flow; AUA-SI = American Urological Association Symptom Index; BC = bladder capacity; BD = bladder dysfunction; Compl. = compliance; DanPSS = Danish prostate symptom score; DC = detrusor contraction; DCA = detrusor contraction amplitude; DO = detrusor overactivity; DPMF = maximum detrusor pressure during maximum flow; DCT = detrusor contraction threshold; ET = essential tremor; FDV = first desire to void; GPi = globus pallidus internus; IPSS = international prostate symptom score; MDP = maximum detrusor pressure; MF = maximum flow; NA = not applicable; NMSQ = non-motor symptoms questionnaire; NMSS = non-motor symptoms scale; NR = not reported; OAB-q = Overactive Bladder Eight Questionnaire; OABSS = overactive bladder symptoms score; PD = Parkinson's disease; PDQ-8 = PD questionnaire-8; PDQ-39 = PD questionnaire-39; PGI-I = patient global impression of improvement score for urinary symptoms; PPN = pedunculopontine nucleus; PVR = post-void residual; QoL = quality of life; SDV = strong desire to void; SHIM = Sexual Health Inventory for Men; STN = subthalamic nucleus; VIM = ventral intermediate nucleus of the thalamus; VV = voided volume.

2.4. Data synthesis

Studies reporting on urodynamic investigations (n = 9) with DBS ON and OFF state were further analyzed. Based on the sample size, mean, and standard deviation of the experimental group and the control group of the included studies, the standardized mean difference and corresponding 95% confidence intervals (CI) were calculated. In cases where median and ranges were reported, mean and standard deviation (SD) were estimated with a previously described method [13]. Due to the lack of RCTs, we assumed that important confounding factors, i.e. different patients' populations and DBS procedures, might have an impact on treatment effects. Thereby, a random effect model was used in the meta-analysis. Forest plots were generated in order to provide a visual representation of the results and to show the direction and magnitude of the effects of DBS in the most prevalent target, i.e. the subthalamic nucleus. Analyses and risk of bias summary and graphs were performed using the Cochrane RevMan software (RevMan v 5.3; Informatics and Knowledge Management Department; Cochrane, St Albans House, 57–59 Haymarket, London, UK).

2.5. Data availability

Data are available to qualified investigators on request to the corresponding author.

3. Results

3.1. Search results

The PRISMA flow diagram chart (Fig. 1) shows the literature search and results. After screening of 577 abstracts, 29 studies were included in the qualitative synthesis, which summarized the studies describing DBS effects on lower urinary tract function. Out of these 29 studies, 9 reported on urodynamic parameters in DBS ON versus DBS OFF and were used for the quantitative analysis. Of the 29 included studies, 25 were prospective cohort studies [9,14–37], two were retrospective cohort studies [38,39], and two were case reports [40,41].

3.2. Study and patient characteristics

Overall, the 29 included studies enrolled a total of 1293 patients: 429 women (33%), 805 men (62%), and 59 patients (5%) for whom the gender was not reported. Patients suffered from PD (n = 1234), dystonia (n = 29), essential tremor (n = 21), or other neurological disorders (n = 9). Patients had leads implanted in either the globus pallidus internus (GPi, n = 100), pedunculopontine nucleus (PPN, n = 6), subthalamic nucleus (STN, n = 1004), or ventral intermediate nucleus of the thalamus (VIM, n = 7). In 123 patients, the lead implantation site was not specified but it was either the GPi, STN, or VIM. Fifty-three patients were in a control group without implanted DBS leads (Table 1). Studies included in the quantitative analysis performed sequential testing, i.e. first DBS ON and 10–30 min later DBS OFF state. In case of PD patients, anti-Parkinsonian drugs were stopped 12 h before testing.

3.3. Efficacy of deep brain stimulation

Treatment outcomes of DBS on lower urinary tract function are shown in Table 2. Urodynamic parameters are based on the total number of recruited patients except for 23 patients being excluded for the following reasons: technical issues in 1 patient [28], refusal of urodynamic investigation in 15 patients [35], and impossibility of spontaneous voiding in 7 patients [30]. DBS of the GPi, PPN, and STN had an inhibitory effect on detrusor function, while DBS of the VIM exhibited an excitatory effect. In the meta-analysis (Fig. 2), DBS of the STN led to a significant increase in maximum bladder capacity (mean difference 124 mL, 95% confidence interval 60–187 mL, p = 0.0001) but had no

Table 2
Treatment outcomes of included studies.

Study	Stimulation site (Neurological disorder)	No. of patients	First desire to void [mL]			Strong desire to void [mL]			Maximum bladder capacity [mL]			Maximum detrusor pressure [cmH_2O]			Detrusor pressure during maximum flow rate [cmH_2O]			Average flow rate [mL/s]			Maximum flow rate [mL/s]			Post-void residual [mL]		
			OFF	ON	Diff.	OFF	ON	Diff.	OFF	ON	Diff.	OFF	ON	Diff.	OFF	ON	Diff.	OFF	ON	DIFF.	OFF	ON	Diff.	OFF	ON	Diff.
Finazzi-Agrò [18]	STN (PD)	5							193.8	327.5	133.7				39.3	39.5	0.2				11.8	11	−0.8			
Herzog [20]	STN (PD)	11	78.9	140	61.1	135.5	199.5	64																		
Herzog [21]	STN (PD)	9	124.4	166.6	42.2	200	286.7	86.7																		
Kessler [23]	VIM (ET)	7	303.8	213	−90.8	375	285	−90	403.8	312.5	−91.3	57.3	58.3	1	46.5	48.3	1.8				11.8	11.3	−0.5	66.3	35	−31.3
Mordasini [25]	GPi (Dystonia)	11	237	272	35	331	397	66	395	443	48	44	39	−5	31	31	0				14	12	−2	43	96	53
Roy [28]	PPN (PD)	5	53.8	91.4	37.6				131	199	68	23	32	9												
Seif [30]	STN (PD)	9	135	199	64				174	302	128										11	13	2	114	71	−43
Shimizu [31]	STN (PD)	6							104	177.2	73.2				60.5	51.3	−9.2				8.8	9.4	0.6	45.2	31.2	−14
Yamamoto [35]	STN, GPi (PD)	13	134.7	108.2	−26.5	234.8	226.7	−8.1										3.40	3.14	−0.26	8.4	7.57	−0.83	28.5	42	13.5

ET = essential tremor; GPi = globus pallidus internus; PD = Parkinson's disease; PPN = pedunculopontine nucleus; STN = subthalamic nucleus; VIM = ventral intermediate nucleus of the thalamus.

relevant effects on the volume at first and strong desire to void, the maximum flow rate, the detrusor pressure during maximum flow rate, or the post-void residual.

3.4. Safety of deep brain stimulation

Thirteen of the 29 included studies reported adverse events (Table 1) possibly related to DBS procedures, and these were most commonly wound healing disturbance, respiratory issues, postural instability, and dysphagia.

3.5. Risk of bias and confounding

The overall risk of bias and confounding was relatively low (Supplement 2a and 2b). Nevertheless, less than 50% of the studies reported the DBS stimulation parameters and for more than 60% of the studies was not clear if the participants were recruited consecutively or selectively chosen. Two studies disclosed a conflict of interest [16,41] and one reported on the role of the funding source [16].

4. Discussion

4.1. Principal findings

Our findings indicate that DBS in the treatment of movement disorders does not impair lower urinary tract function and might even have a beneficial impact. DBS of the GPi, PPN, or STN had an inhibitory effect on detrusor function (increase of bladder capacity in patients with low bladder capacity), while DBS of the VIM showed the opposite (decrease of bladder capacity in patients with high bladder capacity). The number of reported severe adverse events directly related to the therapy was very limited, demonstrating a favorable safety profile.

4.2. Findings in the context of existing evidence

Despite the wide use of DBS, our knowledge on its effects on autonomic symptoms, especially also on the lower urinary tract function, is very limited. Improvements in bladder function have been observed in PD patients subjected to DBS of the STN. It has been hypothesized that the beneficial effects may be attributed to an improved integration of bladder afferent signals via the basal ganglia, which in turn can modulate the lateral frontal cortex and the anterior cingulate cortex [20,21]. In DBS of the GPi, PPN, and VIM, the basal ganglia, cortical, subcortical, and thalamic regions seem to be relevant for the impact on lower urinary tract function, although the mode of action remains unclear.

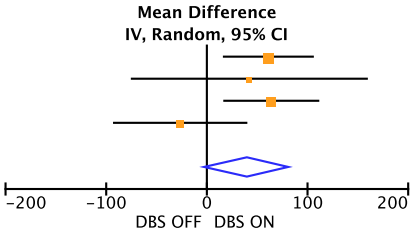
4.3. Implications

The findings of our systematic review suggest benefits and a favorable safety profile of DBS for treating NLUTD in patients affected by movement disorders via modulation of basal-ganglia-thalamo-cingulocortical pathways depending on the brain target. However, our insights are limited by restricted research opportunities in humans. Animal models are therefore required to develop novel treatment options, to expand our knowledge, and to finally improve the quality of life of our patients. Indeed, DBS in animals showed relevant effects on lower urinary tract function depending on the stimulation site similar to our findings in humans [42–44]. Thus, DBS might be used to treat storage and voiding dysfunction of the lower urinary tract, i.e. overactive bladder syndrome (by detrusor relaxation and increasing low bladder capacity via inhibitory DBS effects) and urinary retention (by detrusor stimulation and decreasing high bladder capacity via excitatory DBS effects).

A. First desire to void

Study or Subgroup	DBS ON Mean	SD	Total	DBS OFF Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Herzog 2006	140	65.1	11	78.9	36.6	11	34.0%	61.10 [16.97, 105.23]
Herzog 2008	166.6	132.1	9	124.4	120.2	9	10.3%	42.20 [−74.48, 158.88]
Seif 2004	199	57	9	135	43	9	32.5%	64.00 [17.35, 110.65]
Yamamoto 2018	108.2	57.3	13	134.7	106.36	13	23.2%	−26.50 [−92.17, 39.17]
Total (95% CI)			**42**			**42**	**100.0%**	**39.77 [−1.81, 81.36]**

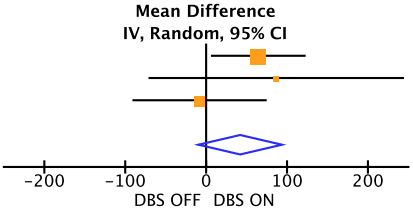
Heterogeneity: Tau² = 817.92; Chi² = 5.70, df = 3 (P = 0.13); I² = 47%
Test for overall effect: Z = 1.87 (P = 0.06)



B. Strong desire to void

Study or Subgroup	DBS ON Mean	SD	Total	DBS OFF Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Herzog 2006	199.5	72.1	11	135	64.6	11	57.1%	64.50 [7.29, 121.71]
Herzog 2008	286.7	178.8	9	200	159.6	9	10.1%	86.70 [−69.88, 243.28]
Yamamoto 2018	226.7	77.5	13	234.8	128.7	13	32.8%	−8.10 [−89.77, 73.57]
Total (95% CI)			**33**			**33**	**100.0%**	**42.94 [−8.24, 94.12]**

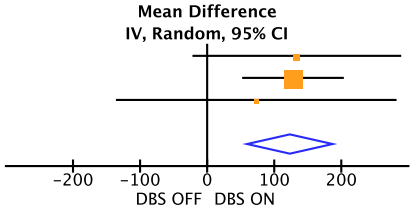
Heterogeneity: Tau² = 343.20; Chi² = 2.34, df = 2 (P = 0.31); I² = 15%
Test for overall effect: Z = 1.64 (P = 0.10)



C. Maximum bladder capacity

Study or Subgroup	DBS ON Mean	SD	Total	DBS OFF Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Finazzi-Agrò 2003	327.5	97.5	5	193.8	146.2	5	17.1%	133.70 [−20.33, 287.73]
Seif 2004	302	101	9	174	52	9	73.5%	128.00 [53.78, 202.22]
Shimizu 2007	177.2	161.2	6	104	203.4	6	9.4%	73.20 [−134.47, 280.87]
Total (95% CI)			**20**			**20**	**100.0%**	**123.83 [60.18, 187.47]**

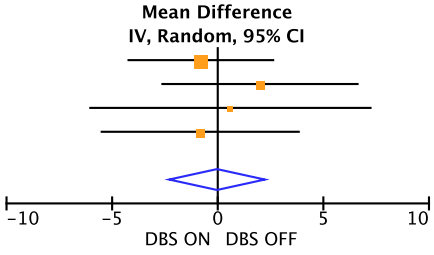
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 2 (P = 0.88); I² = 0%
Test for overall effect: Z = 3.81 (P = 0.0001)



D. Maximum flow rate

Study or Subgroup	DBS ON Mean	SD	Total	DBS OFF Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Finazzi-Agrò 2003	11	2.5	5	11.8	3	5	42.5%	−0.80 [−4.22, 2.62]
Seif 2004	13	5	9	11	5	9	23.3%	2.00 [−2.62, 6.62]
Shimizu 2007	9.4	5.5	6	8.8	6.2	6	11.3%	0.60 [−6.03, 7.23]
Yamamoto 2018	7.57	5.1	13	8.4	6.9	13	22.9%	−0.83 [−5.49, 3.83]
Total (95% CI)			**33**			**33**	**100.0%**	**0.00 [−2.23, 2.24]**

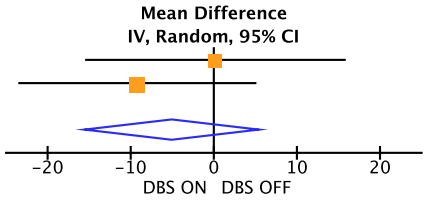
Heterogeneity: Tau² = 0.00; Chi² = 1.08, df = 3 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)



E. Detrusor pressure during maximum flow rate

Study or Subgroup	DBS ON Mean	SD	Total	DBS OFF Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Finazzi-Agrò 2003	39.5	13.6	5	39.3	11.4	5	45.5%	0.20 [−15.35, 15.75]
Shimizu 2007	51.3	13.6	6	60.5	11.4	6	54.5%	−9.20 [−23.40, 5.00]
Total (95% CI)			**11**			**11**	**100.0%**	**−4.93 [−15.41, 5.56]**

Heterogeneity: Tau² = 0.00; Chi² = 0.77, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 0.92 (P = 0.36)



F. Post-void residual

Study or Subgroup	DBS ON Mean	SD	Total	DBS OFF Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Seif 2004	71	33	9	114	37	9	44.3%	−43.00 [−74.06, −11.94]
Shimizu 2007	31.2	92	5	45.2	86.1	5	14.2%	−14.00 [−114.82, 86.82]
Yamamoto 2018	42	51.6	13	28.5	39.7	13	41.5%	13.50 [−21.89, 48.89]
Total (95% CI)			**30**			**28**	**100.0%**	**−15.42 [−59.33, 28.50]**

Heterogeneity: Tau² = 883.10; Chi² = 5.54, df = 2 (P = 0.06); I² = 64%
Test for overall effect: Z = 0.69 (P = 0.49)

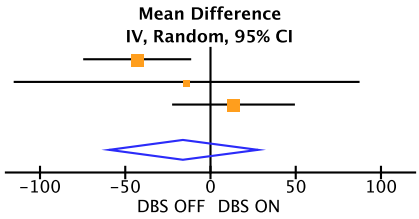


Fig. 2. Effects of deep brain stimulation of the subthalamic nucleus (STN) on urodynamic parameters in Parkinson's disease patients. A) Bladder volume at first desire to void (mL); B) Bladder volume at strong desire to void (mL); C) Maximum bladder capacity (mL); D) Maximum flow rate (mL/s); E) Detrusor pressure during maximum flow rate (cmH_2O); F) Post-void residual (mL). Data are shown as mean difference with 95% confidence interval. Positive values indicate an increase, negative values a decrease.

4.4. Limitations of this study

Although we present to the best of our knowledge the first systematic review synthesizing all available evidence of DBS effects on lower urinary tract function, there are limitations that should be addressed. Included papers are mostly small cohort studies with a low number of patients with a before-and-after treatment design, and only the study by Rukmini Mridula et al. [29] had a comparator. We aimed to perform subgroup analyses for different neurological diseases and stimulation sites, but 94% of the subjects suffered from PD and had DBS leads implanted in either the STN or, less frequently, the GPi. DBS stimulation parameters were not always reported, which may have an impact on our findings as we could not control for this potentially highly relevant covariate. In addition, several studies described changes in lower urinary tract function using a subjective scoring system not allowing for data pooling due to heterogenous outcomes. Two studies [43,45] investigated DBS for treating NLUTD, but raw data were not available. Nevertheless, the overall risk of bias and confounding of the included studies was relatively low.

4.5. Future directions

Based on our findings, well-designed and powered prospective clinical studies investigating DBS effects on lower urinary tract function using patient-reported outcomes (i.e. bladder diaries and validated questionnaires) as well as clinical assessment tools (i.e. free uroflowmetry, post-void residual measurement, and video-urodynamics) are highly warranted. These studies should consider and balance differences in stimulation sites and stimulation parameters but also taking into account the varieties of the neurological disorders treated by DBS.

5. Conclusions

DBS does not impair lower urinary tract function and might even have beneficial effects. This is highly relevant for counselling patients in the informed consent procedure considering DBS and needs to be taken into account in the decision-making process helping to encourage and to reassure prospective patients.

Contributors

EJ, AMS, and TMK created the study design. EJ and AMS analyzed the data. EJ, AMS, and TMK drafted the manuscript. AH and CRB critically reviewed the manuscript. All the authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2020.08.032.

References

[1] A.S. Burns, D.A. Rivas, J.F. Ditunno, The management of neurogenic bladder and sexual dysfunction after spinal cord injury, Spine 26 (24 Suppl) (2001) S129–S136.
[2] R.N. Campos-Sousa, E. Quagliato, B.B. da Silva, R.M. de Carvalho Jr., S.C. Ribeiro, D.F. de Carvalho, Urinary symptoms in Parkinson's disease: Prevalence and associated factors, Arquivos de neuro-psiquiatria 61 (2b) (2003) 359–363.
[3] A. Giannantoni, G. Scivoletto, S.M. Di Stasi, M.G. Grasso, E. Finazzi Agro, G. Collura, G. Vespasiani, Lower urinary tract dysfunction and disability status in patients with multiple sclerosis, Arch. Phys. Med. Rehabil. 80 (4) (1999) 437–441.
[4] J.N. Panicker, C.J. Fowler, T.M. Kessler, Lower urinary tract dysfunction in the neurological patient: Clinical assessment and management, The Lancet, Neurology 14 (7) (2015) 720–732.
[5] M. Ferrarin, M. Rizzone, B. Bergamasco, M. Lanotte, M. Recalcati, A. Pedotti, L. Lopiano, Effects of bilateral subthalamic stimulation on gait kinematics and kinetics in Parkinson's disease, Exp. Brain Res. 160 (4) (2005) 517–527.
[6] W. Ondo, J. Jankovic, K. Schwartz, M. Almaguer, R.K. Simpson, Unilateral thalamic deep brain stimulation for refractory essential tremor and Parkinson's disease tremor, Neurology 51 (4) (1998) 1063–1069.
[7] A. Alamri, I. Ughratdar, M. Samuel, K. Ashkan, Deep brain stimulation of the subthalamic nucleus in Parkinson's disease 2003-2013: Where are we another 10 years on? Br. J. Neurosurg. 29 (3) (2015) 319–328.
[8] R. Constantinescu, B. Eriksson, Y. Jansson, B. Johnels, B. Holmberg, T. Gudmundsdottir, A. Renck, P. Berglund, F. Bergquist, Key clinical milestones 15 years and onwards after DBS-STN surgery-A retrospective analysis of patients that underwent surgery between 1993 and 2001, Clin. Neurol. Neurosurg. 154 (2017) 43–48.
[9] S. Mock, D.J. Osborn, E.T. Brown, W. Stuart Reynolds, M. Turchan, S. Pallavaram, W. Rodriguez, R. Dmochowski, C.M. Tolleson, The impact of pallidal and subthalamic deep brain stimulation on urologic function in Parkinson's disease, neuromodulation, journal of the International Neuromodulation Society 19 (7) (2016) 717–723.
[10] J. Dulski, M. Schinwelski, A. Konkel, K. Grabowski, W. Libionka, P. Waz, E.J. Sitek, J. Slawek, The impact of subthalamic deep brain stimulation on sleep and other non-motor symptoms in Parkinson's disease, Park. Relat. Disord. 64 (2019) 138–144.
[11] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, Ann. Intern. Med. 151 (4) (2009) 264–269, w64.
[12] M. Viswanathan, M.T. Ansari, N.D. Berkman, S. Chang, L. Hartling, M. McPheeters, P.L. Santaguida, T. Shamliyan, K. Singh, A. Tsertsvadze, J.R. Treadwell, AHRQ Methods for Effective Health Care Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions, Methods Guide for Effectiveness and Comparative Effectiveness Reviews, Agency for Healthcare Research and Quality (US), Rockville (MD), 2008.
[13] X. Wan, W. Wang, J. Liu, T. Tong, Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range, BMC Med. Res. Methodol. 14 (2014) 135.
[14] H.S. Dafsari, P. Reddy, C. Herchenbach, S. Wawro, J.N. Petry-Schmelzer, V. Visser-Vandewalle, A. Rizos, M. Silverdale, K. Ashkan, M. Samuel, J. Evans, C.A. Huber, G.R. Fink, A. Antonini, K.R. Chaudhuri, P. Martinez-Martin, L. Timmermann, Beneficial effects of bilateral subthalamic stimulation on non-motor symptoms in Parkinson's disease, Brain stimulation 9 (1) (2016) 78–85.
[15] H.S. Dafsari, M. Silverdale, M. Strack, A. Rizos, K. Ashkan, P. Mahlstedt, L. Sachse, J. Steffen, T.A. Dembek, V. Visser-Vandewalle, J. Evans, A. Antonini, P. Martinez-Martin, K. Ray-Chaudhuri, L. Timmermann, Nonmotor symptoms evolution during 24 months of bilateral subthalamic stimulation in Parkinson's disease, Movement disorders, official journal of the Movement Disorder Society 33 (3) (2018) 421–430.
[16] H.S. Dafsari, L. Weiss, M. Silverdale, A. Rizos, P. Reddy, K. Ashkan, J. Evans, P. Reker, J.N. Petry-Schmelzer, M. Samuel, V. Visser-Vandewalle, A. Antonini, P. Martinez-Martin, K. Ray-Chaudhuri, L. Timmermann, Short-term quality of life after subthalamic stimulation depends on non-motor symptoms in Parkinson's disease, Brain Stimul 11 (4) (2018) 867–874.
[17] H.S. Dafsari, P. Martinez-Martin, A. Rizos, M. Trost, M.G. Dos Santos Ghilardi, P. Reddy, A. Sauerbier, J.N. Petry-Schmelzer, M. Kramberger, R.W. K. Borgemeester, M.T. Barbe, K. Ashkan, M. Silverdale, J. Evans, P. Odin, E. T. Fonoff, G.R. Fink, T. Henriksen, G. Ebersbach, Z. Pirtošek, V. Visser-Vandewalle, A. Antonini, L. Timmermann, K. Ray Chaudhuri, EuroInf 2: Subthalamic stimulation, apomorphine, and levodopa infusion in Parkinson's disease, Mov. Disord. 34 (3) (2019) 353–365.
[18] E. Finazzi-Agro, A. Peppe, A. D'Amico, F. Petta, P. Mazzone, P. Stanzione, F. Micali, C. Caltagirone, Effects of subthalamic nucleus stimulation on urodynamic findings in patients with Parkinson's disease, J. Urol. 169 (4) (2003) 1388–1391.
[19] A. Halim, L. Baumgartner, D.K. Binder, Effect of deep brain stimulation on autonomic dysfunction in patients with Parkinson's disease, J. Clin. Neurosci. 18 (6) (2011) 804–806.
[20] J. Herzog, P.H. Weiss, A. Assmus, B. Wefer, C. Seif, P.M. Braun, H. Herzog, J. Volkmann, G. Deuschl, G.R. Fink, Subthalamic stimulation modulates cortical control of urinary bladder in Parkinson's disease, Brain : J. Neurol. 129 (Pt 12) (2006) 3366–3375.
[21] J. Herzog, P.H. Weiss, A. Assmus, B. Wefer, C. Seif, P.M. Braun, M.O. Pinsker, H. Herzog, J. Volkmann, G. Deuschl, G.R. Fink, Improved sensory gating of urinary bladder afferents in Parkinson's disease following subthalamic stimulation, Brain : J. Neurol. 131 (Pt 1) (2008) 132–145.
[22] N. Hwynn, I. Ul Haq, I.A. Malaty, A.S. Resnick, Y. Dai, K.D. Foote, H.H. Fernandez, S.S. Wu, G. Oyama, C.E.t. Jacobson, S.K. Kim, M.S. Okun, Effect of Deep Brain Stimulation on Parkinson's Nonmotor Symptoms Following Unilateral DBS: A Pilot Study, Parkinson's Disease 2011, 2011, p. 507416.
[23] T.M. Kessler, F.C. Burkhard, S. Z'Brun, A. Stibal, U.E. Studer, C.W. Hess, A. Kaelin-Lang, Effect of thalamic deep brain stimulation on lower urinary tract function, Eur. Urol. 53 (3) (2008) 607–612.
[24] A. Merola, M. Zibetti, S. Angrisano, L. Rizzi, V. Ricchi, C.A. Artusi, M. Lanotte, M. G. Rizzone, L. Lopiano, Parkinson's disease progression at 30 years: A study of subthalamic deep brain-stimulated patients, Brain : J. Neurol. 134 (Pt 7) (2011) 2074–2084.

[25] L. Mordasini, T.M. Kessler, B. Kiss, M. Schupbach, C. Pollo, A. Kaelin-Lang, Bladder function in patients with dystonia undergoing deep brain stimulation, Park. Relat. Disord. 20 (9) (2014) 1015–1017.
[26] K. Nakamura, Y. Yamanaka, Y. Higuchi, S. Hirano, R. Kuroiwa, M. Abe, A. Murata, Y. Iwadate, S. Kuwabara, T. Yamamoto, Improved self-perceived performance for continence problems in patients with Parkinson's disease after deep brain stimulation, Neurology and Clinical Neuroscience 7 (2) (2019) 51–56.
[27] W. Pietraszko, A. Furgala, A. Gorecka-Mazur, P. Thor, M. Moskala, J. Polak, A. D. Surowka, A. Krygowska-Wajs, Efficacy of deep brain stimulation of the subthalamic nucleus on autonomic dysfunction in patients with Parkinson's disease, Folia Med. Cracov. 53 (2) (2013) 15–22.
[28] H.A. Roy, D. Pond, C. Roy, B. Forrow, T. Foltynie, L. Zrinzo, H. Akram, T.Z. Aziz, J. J. FitzGerald, A.L. Green, Effects of pedunculopontine nucleus stimulation on human bladder function, Neurourol. Urodyn. 37 (2) (2018) 726–734.
[29] K. Rukmini Mridula, R. Borgohain, S.A. Jabeen, G. Padmaja, V.S. Bandaru, P. Ankathi, M.A. Kanikannan, M.S. Ali Khan, Comparison of frequencies of non motor symptoms in Indian Parkinson's disease patients on medical management versus deep brain stimulation: a case-control study, Iranian journal of neurology 14 (2) (2015) 86–93.
[30] C. Seif, J. Herzog, C. van der Horst, B. Schrader, J. Volkmann, G. Deuschl, K. P. Juenemann, P.M. Braun, Effect of subthalamic deep brain stimulation on the function of the urinary bladder, Ann. Neurol. 55 (1) (2004) 118–120.
[31] N. Shimizu, S. Matsumoto, Y. Mori, N. Yoshioka, H. Uemura, N. Nakano, M. Taneda, [Effects of deep brain stimulation on urodynamic findings in patients with Parkinson's disease], Hinyokika kiyo, Acta Urol. Jpn. 53 (9) (2007) 609–612.
[32] K. Winge, K.K. Nielsen, Bladder dysfunction in advanced Parkinson's disease, Neurourology and urodynamics 31 (8) (2012) 1279–1283.
[33] L.P. Witte, V.J.J. Odekerken, J.A. Boel, P.R. Schuurman, L.C. Gerbrandy-Schreuders, R.M.A. de Bie, Does deep brain stimulation improve lower urinary tract symptoms in Parkinson's disease? Neurourol. Urodyn. 37 (1) (2017) 354–359.
[34] M. Wolz, J. Hauschild, J. Koy, M. Fauser, L. Klingelhofer, G. Schackert, H. Reichmann, A. Storch, Immediate effects of deep brain stimulation of the subthalamic nucleus on nonmotor symptoms in Parkinson's disease, Park. Relat. Disord. 18 (8) (2012) 994–997.
[35] T. Yamamoto, T. Uchiyama, M. Asahina, Y. Yamanaka, S. Hirano, Y. Higuchi, S. Kuwabara, Urinary symptoms are correlated with quality of life after deep brain stimulation in Parkinson's disease, Brain Behav 8 (12) (2018), e01164.
[36] M. Zibetti, E. Torre, A. Cinquepalmi, M. Rosso, A. Ducati, B. Bergamasco, M. Lanotte, L. Lopiano, Motor and nonmotor symptom follow-up in parkinsonian patients after deep brain stimulation of the subthalamic nucleus, Eur. Neurol. 58 (4) (2007) 218–223.
[37] H. Zong, F. Meng, Y. Zhang, G. Wei, H. Zhao, Clinical study of the effects of deep brain stimulation on urinary dysfunctions in patients with Parkinson's disease, Clin. Interv. Aging 14 (2019) 1159–1166.
[38] C. Buhmann, T. Huckhagel, K. Engel, A. Gulberti, U. Hidding, M. Poetter-Nerger, I. Goerendt, P. Ludewig, H. Braass, C.U. Choe, K. Krajewski, C. Oehlwein, K. Mittmann, A.K. Engel, C. Gerloff, M. Westphal, J.A. Koppen, C.K.E. Moll, W. Hamel, Adverse events in deep brain stimulation: A retrospective long-term analysis of neurological, psychiatric and other occurrences, PloS One 12 (7) (2017), e0178984.
[39] J.M. Nazzaro, R. Pahwa, K.E. Lyons, The impact of bilateral subthalamic stimulation on non-motor symptoms of Parkinson's disease, Park. Relat. Disord. 17 (8) (2011) 606–609.
[40] I. Aviles-Olmos, T. Foltynie, J. Panicker, D. Cowie, P. Limousin, M. Hariz, C. J. Fowler, L. Zrinzo, Urinary incontinence following deep brain stimulation of the pedunculopontine nucleus, Acta Neurochir. 153 (12) (2011) 2357–2360.
[41] F.T. Liu, L.Q. Lang, R.Y. Zhou, R. Feng, J. Hu, J. Wang, J.J. Wu, Urinary incontinence following deep brain stimulation of the globus pallidus internus: Case report, J. Neurosurg. (2019) 1–3.
[42] S.C. Chen, P.Y. Chu, T.H. Hsieh, Y.T. Li, C.W. Peng, Feasibility of deep brain stimulation for controlling the lower urinary tract functions: An animal study, Clin. Neurophysiol. 128 (12) (2017) 2438–2449.
[43] A.L. Green, E. Stone, H. Sitsapesan, B.W. Turney, J.H. Coote, T.Z. Aziz, J.A. Hyam, T.A. Lovick, Switching off micturition using deep brain stimulation at midbrain sites, Ann. Neurol. 72 (1) (2012) 144–147.
[44] E. Stone, J.H. Coote, T.A. Lovick, Effect of electrical vs. chemical deep brain stimulation at midbrain sites on micturition in anaesthetized rats, Acta Physiol. 214 (1) (2015) 135–145.
[45] K. Winge, K.K. Nielsen, H. Stimpel, A. Lokkegaard, S.R. Jensen, L. Werdelin, Lower urinary tract symptoms and bladder control in advanced Parkinson's disease: Effects of deep brain stimulation in the subthalamic nucleus, Movement disorders. 22 (2) (2007) 220–225.