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Beta oscillations and urinary voiding in Parkinson disease

Holly A. Roy, BMBCh, MRCS, Tipu Z. Aziz, FRCS(SN), FMedSci, James J. Fitzgerald, PhD, FRCS(SN), and Alexander L. Green, MD, FRCS(SN)

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Correspondence
Holly A. Roy
roy.hollyann@gmail.com

Abstract

Objectives

To investigate the role of beta oscillations in urinary voiding and their association with lower urinary tract symptoms in Parkinson disease (PD).

Methods

We used surgically implanted deep brain stimulation electrodes to record local field potential signals from the subthalamic nucleus (STN) and globus pallidus interna (GPi) of patients with PD during urinary voiding. Five patients with STN electrodes and 5 patients with GPi electrodes were tested. We also explored correlations between beta oscillatory power and urinary symptoms assessed by the International Consultation on Incontinence Lower Urinary Tract Symptoms questionnaire.

Results

Beta suppression occurred during urinary voiding in the GPi ($p < 0.05$) but not the STN. Furthermore, the beta signal in the GPi during voiding correlated significantly with severity of incontinence and urinary frequency ($p < 0.05$).

Conclusions

In this study, we have demonstrated that local field potentials can provide information about the neural control of the bladder. Our findings suggest that the GPi is implicated in the process of urinary voiding and that its mechanism of action is linked to signals in the beta frequency band. Moreover, our correlational analyses show that beta oscillations may be implicated more generally in the pathophysiology of lower urinary tract symptoms in PD.

From the Department of Functional Neurosurgery (H.A.R., T.Z.A., J.J.F., A.L.G.) and Nuffield Department of Surgical Sciences (H.A.R., T.Z.A., J.J.F., A.L.G.), John Radcliffe Hospital, Oxford; and Department of Neurosurgery (H.A.R.), Derriford Hospital, Plymouth, UK.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

DBS = deep brain stimulation; **GPi** = globus pallidus interna; **ICIQ** = International Consultation on Incontinence Questionnaire; **LFP** = local field potential; **PD** = Parkinson disease; **STN** = subthalamic nucleus.

Lower urinary tract symptoms occur in up to 75% of patients with Parkinson disease (PD) and include storage symptoms (frequency, nocturia, urgency, and incontinence) and voiding symptoms (hesitancy and interrupted voiding).[1] To further understand the role of the basal ganglia in lower urinary tract function in PD, we recorded local field potentials (LFPs) from deep brain stimulation (DBS) electrodes implanted within the subthalamic nucleus (STN) and globus pallidus interna (GPi) of patients with PD during micturition. LFP signals represent the averaged oscillatory activity of the neuronal population within 1 to 2 mm of the DBS electrode tip and provide information about local neuronal inputs and integrative processing.[2] Beta suppression within the basal ganglia occurs with voluntary movement,[3] and beta oscillations are also associated with motor symptoms in PD.[4] We hypothesized that beta oscillations would be implicated in urinary control in an analogous way.

Methods

Participants

A total of 13 participants with PD who had been chosen to undergo DBS for their motor symptoms were recruited to the study: 7 with STN electrodes (12 nuclei) and 6 with GPi electrodes (11 nuclei). Consecutive patients undergoing DBS of the STN or GPi were approached to participate. (The allocation to STN or GPi DBS was based on clinical factors before recruitment to the study.) Recruitment took place between November 2014 and November 2015, and the study was carried out in the Neurosciences department at the John Radcliffe Hospital. On the basis of our previous LFP studies, we calculated that we would require a minimum of 5 patients to determine a beta change of 20%. All participants completed an International Consultation on Incontinence Questionnaire (ICIQ) on lower urinary tract symptoms.[5]

Standard protocol approvals, registrations, and patient consents

The study was carried out in accordance with the Declaration of Helsinki and received approval from the Oxfordshire Research Ethics Committee B (study 09/H0605/62). All participants provided consent to participate in the study.

Experimental paradigm

Participants were asked to attend with a full bladder and to take their normal PD medications (i.e., patients were tested "on" medication). Testing was performed 3 to 6 days after implantation of the DBS electrode, when the system was still externalized and available for recording.

LFP recordings were made during at least 2 separate 30-second trials of quiet rest with eyes closed. Participants were then asked to void urine. The experimenter indicated when the patients should start attempting to void with a verbal start cue. The time of onset and cessation of urine flow was recorded by the experimenter. If the void was >10 seconds in duration, the participant was asked to interrupt the void and to restart voiding after a 10-second pause.

LFP recordings

With the exception of participants 9 and 10, all study participants had quadripolar macroelectrodes implanted (Medtronic 3389 for patients with STN electrodes and 3387 for patients with GPi electrodes). Participants 9 and 10 had Boston Scientific 8-contact electrodes implanted. LFPs were recorded from externalized DBS electrodes with a portable physiologic measuring system (Porti 7, TMS International, Zevenhuizen, the Netherlands) and sampled at 2,048 Hz. A ground electrode was placed on the dorsum of the participant's wrist, and a common average reference was used.

Signal analysis

Signals were analyzed offline with Spike2 software and the NSPL toolbox (Shouyan Wang) in MATLAB (MathWorks, Inc, Natick, MA).

Electrode locations were examined with image fusion software (Neuroinspire, Renishaw plc, Wotton-Under-Edge, Gloucestershire, UK) to display the electrode contacts identifiable on postoperative CT, superimposed on the preoperative MRI scan, by one of the experimenters who were experienced at anatomically locating the STN and GPi (A.L.G.), and the electrode contacts within the structure of interest were identified. Bipolar channels were then created by subtracting the signal in the contact of interest from that of an adjacent contact.

The signal was down-sampled to 1,000 Hz and exported to NSPL. Bipolar signals were low-pass filtered at 200 Hz, high-pass filtered at 2 Hz, and band-stop filtered at 50 Hz with a Butterworth filter to exclude mains artifact.

Power spectral density analysis was performed on 10-second data segments of rest and void trials with a 1.5-second Hanning window. Power spectral density was computed from an algorithm within the NSPL program that integrated the power in the spectra within user-selected frequency bands. Signals in the beta band (12–25 Hz) were calculated for further analysis.

Statistical analysis

STN and GPi data were analyzed separately. Beta power in rest and void trials was averaged across trials for each patient

and compared by use of nonparametric statistics (Wilcoxon signed-rank test).

For the correlational analyses, a normalized void signal was created by dividing the signal during each void trial with the baseline signal during rest. Correlations between ICIQ scores and normalized power during void were made with the averaged normalized void power across all void trials for each nucleus. The Pearson correlation (2 tailed) was used for correlational analyses. All significance levels were set at $p < 0.05$.

Results

Five participants with STN electrodes (3 male, 2 female, 8 nuclei) and 5 participants with GPi electrodes (4 male, 1 female, 9 nuclei) were able to void urine under experimental conditions (see the table for further information). Data from those participants unable to void were not analyzed further.

Signal changes during urinary voiding

In the GPi, there was a decrease in beta power during urinary voiding relative to rest ($p = 0.011$) (figure 1). In the STN, there was no difference in beta power during urinary voiding relative to rest (figure 1).

Clinical correlations

ICIQ scores obtained from participant questionnaires were broken down into voiding, frequency, and incontinence components as directed by the questionnaire, and correlations with the normalized LFP signal were explored. There was a positive correlation between normalized GPi beta power during voiding and both the ICIQ incontinence score ($p = 0.005$) and frequency score ($p = 0.014$) but not the voiding score (figure 2). There were no correlations between STN beta signal and ICIQ scores.

Discussion

In this study, we have used LFP signatures to examine the relationship between human brain activity and bladder function. Recording from the GPi, we identified suppression of spectral power within the beta band with urinary voiding. Beta suppression frequently occurs with voluntary movement[3]; thus, the beta suppression observed here could be associated with a voluntary component of the micturition process such as relaxation of the external urethral sphincter. Our findings are supported by evidence from neuroimaging and DBS studies that demonstrate pallidal involvement in urinary voiding[6,7] and show that pallidal stimulation significantly reduces the maximal urine flow rate and increases the postvoid residual in patients with dystonia.[8] These findings provide insights into the mechanisms underlying the role of the GPi in bladder control and highlight the GPi as a possible target for bladder neuromodulation.

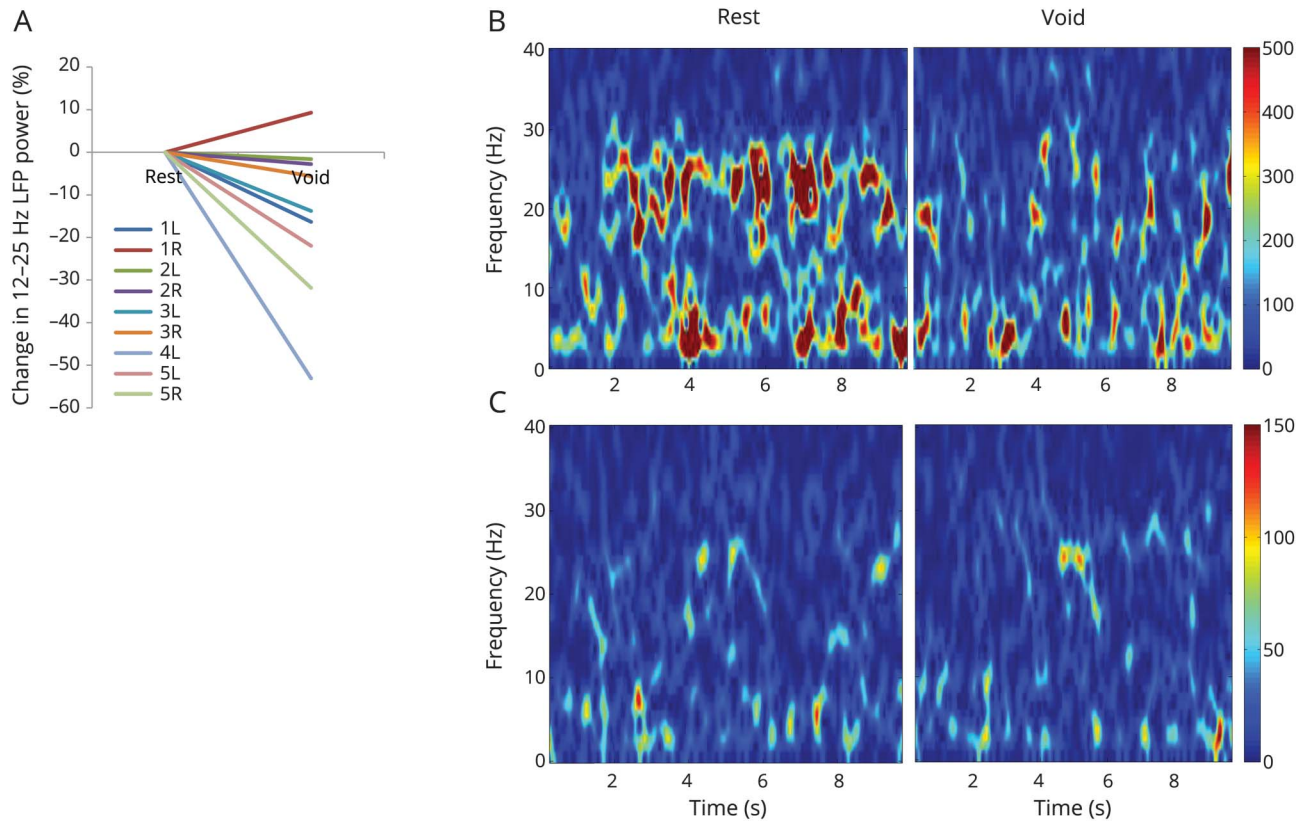
A secondary observation was that the severity of urinary frequency and incontinence correlated positively with the normalized GPi beta signal during voiding. Beta oscillations have previously been linked to motor signs in PD.[4] Failure to effectively suppress beta during voiding may indicate a PD-associated impairment in generalized bladder control. A manifestation of this impoverished control would include incontinence and increased urinary frequency, although it is surprising that correlations with voiding symptoms were not observed. One possible explanation is that voiding symptoms

Table Electrode locations, specifications, demographic details, number of void trials over which LFP data were averaged for each patient, and breakdown of each patient's ICIQ score

Subject	Electrode location and side	Electrode type	Age, y	Sex	Void trials, n	ICIQ score (V/I/F)
1	GPi (L, R)	Medtronic lead 3387	54	M	2	11/8/6
2	GPi (L, R)	Medtronic lead 3387	61	F	2	9/6/9
3	GPi (L, R)	Medtronic lead 3387	58	M	1	1/5/4
4	GPi (L)	Medtronic lead 3387	48	M	1	3/0/1
5	GPi (L, R)	Medtronic lead 3387	58	M	2	2/0/2
6	STN (L, R)	Medtronic lead 3389	71	F	2	7/1/8
7	STN (R)	Medtronic lead 3389	56	F	2	8/4/8
8	STN (R)	Medtronic lead 3389	62	M	2	1/1/0
9	STN (L, R)	BS	48	M	1	4/2/3
10	STN (L, R)	BS	55	M	1	0/2/—

Abbreviations: BS = Boston Scientific; GPi = globus pallidus interna; ICIQ = International Consultation on Incontinence Questionnaire; STN = subthalamic nucleus; V/I/F = voiding/incontinence/frequency.

Figure 1 LFP power during urinary voiding compared to rest

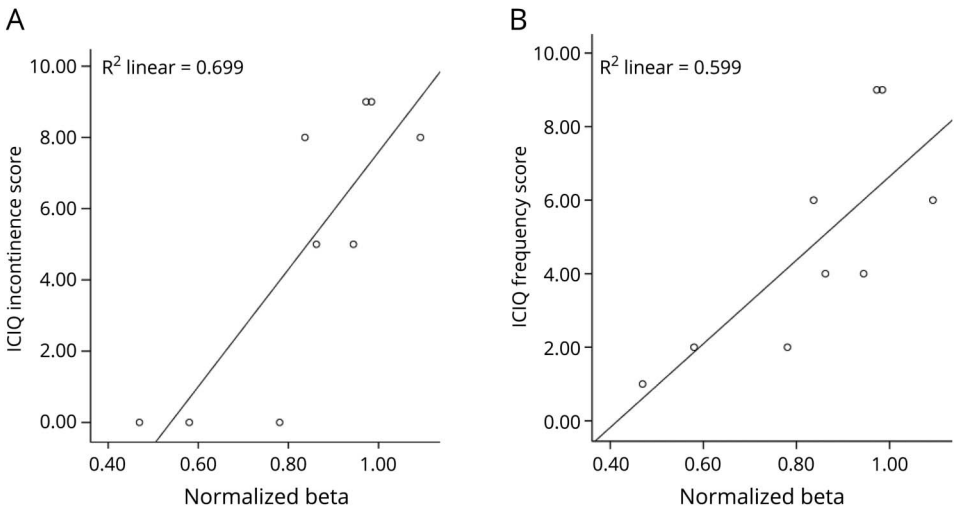


(A) Percent change in 12- to 25-Hz LFP power for each GPi nucleus during void relative to rest. Numbers correspond to the patient numbers in the table. (B) Time-frequency plots during rest and void recorded from the GPi of a single patient demonstrating a reduction in beta frequency power in the void condition. (C) Time-frequency plots during rest and void recorded from the STN of a single patient demonstrating no change in beta frequency power in the void condition. GPi = globus pallidus intern; LFP = local field potential; STN = subthalamic nucleus.

are generally less prominent than storage symptoms in PD, and a sufficient spread in symptom severity was not present within our modest sample size.

We did not observe changes in the STN beta signal with voiding or a correlation between STN beta oscillations and urinary symptoms. The existing literature suggests that the

Figure 2 Correlation between GPi local field potential power and clinical scores



(A) Scatterplot demonstrating a correlation between ICIQ incontinence score and normalized beta power in the GPi during urinary voiding. (B) Correlation between ICIQ frequency score and normalized beta power in the GPi during voiding. GPi = globus pallidus intern; ICIQ = International Consultation on Incontinence.

STN is more closely involved in afferent aspects of urinary regulation during bladder filling[9] rather than motor control during micturition, and DBS at the STN improves bladder capacity but does not affect voiding parameters.[10] Future studies should focus on LFP signal changes within the STN during bladder filling.

A number of limitations are associated with this study. Three participants (2 with STN and 1 with GPi electrodes) were unable to void urine during the trial, and their data were excluded from further analysis, which may be a source of bias. In addition, participants were asked to interrupt their void partway through voiding, which is not physiologic and may have led to results that are not representative of true events that occur during voiding. In future studies, increasing participant numbers may provide sufficient numbers to allow the participants who were unable to void to be analyzed as a separate group.

Although discussions regarding the precise involvement of the STN and GPi in voiding can be only speculative at this stage, our data demonstrate a link between neuronal activity in the GPi and micturition in PD. Further studies that incorporate physiologic adjuncts, including sphincter EMG recordings, will be important to distinguish whether the role of GPi in voiding is important predominantly for controlling the external urethral sphincter, as we have suggested, or another aspect of the voiding process such as regulating inhibitory control of the detrusor muscle. Future studies in participants with GPi electrodes implanted for other indications such as dystonia or Tourette syndrome will help to establish whether the results are generalizable to other populations. Nevertheless, our results raise the possibility that targeted modulation of the GPi through DBS may provide a means of treating voiding dysfunction and incontinence in patients with PD.

Author contributions

H.A.R.: study concept and design, acquisition of data, analysis and interpretation, preparation of manuscript. J.J.F.: critical revision of the manuscript for important intellectual content. T.Z.A.: study supervision, critical revision of the manuscript for important intellectual content. A.L.G.: study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content.

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Disclosure

H.A. Roy and T.Z. Aziz report no disclosures relevant to the manuscript. J.J. Fitzgerald is on a Trial Steering Committee for Abbott and received consultancy fees from Abbott and Boston Scientific. A.L. Green is on an Executive Advisory Board for Abbott and has received consultancy fees from Abbott and Medtronic. Go to Neurology.org/N for full disclosures.

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References

1. Sakakibara R, Panicker J, Finazzi-Agro E, et al. Guideline for the management of bladder dysfunction in Parkinson's disease and other gait disorders. Neurourol Urodyn 2016;35:551–563.
2. Logothetis N, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. Nature 2001;412:150–157.
3. Levy R, Ashby P, Hutchison WD, Lang AE, Lozano AM, Dostrovsky JO. Dependence of subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease. Brain 2002;125:1196–1209.
4. Neumann WJ, Degen K, Schnelder GH, et al. Subthalamic synchronized oscillatory activity correlates with motor impairment in patients with Parkinson's disease. Mov Disord 2016;31:1748–1751.
5. Abrams P, Avery K, Gardener N, Donovan J. The International Consultation on Incontinence Modular Questionnaire: www.iciq.net. J Urol 2006;175:1063–1066.
6. Nour S, Svarer C, Kristensen JKI, Paulson OB, Law I. Cerebral activation during micturition in normal men. Brain 2000;123:781–789.
7. Shy M, Fung S, Boone TB, Karmonik C, Fletcher SG, Khavari R. Functional magnetic resonance imaging during urodynamic testing identifies brain structures initiating micturition. J Urol 2004;192:1149–1154.
8. Mordasini L, Kessler T, Kiss B, Schupbacg M, Pollo C, Kaelin-Lang A. Bladder function in patients with dystonia undergoing deep brain stimulation. Parkinsonism Relat Disord 2014;20:1015–1017.
9. Herzog J, Weiss PH, Assmus A, et al. Improved sensory gating of urinary bladder afferents in Parkinson's disease following subthalamic nucleus stimulation. Brain 2008;131:132–145.
10. Seif C, Herzog J, van der Horst C, et al. Effect of subthalamic deep brain stimulation on the function of the urinary bladder. Ann Neurol 2004;55:118–120.

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Holly A. Roy, BMBCh, MRCS, Tipu Z. Aziz, FRCS(SN), FMedSci, James J. Fitzgerald, PhD, FRCS(SN), and Alexander L. Green, MD, FRCS(SN)

Correspondence
Dr. Roy
roy.hollyann@gmail.com

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Study question

Are beta oscillations related to urinary control in patients with Parkinson disease (PD)?

Summary answer

Beta oscillations in the globus pallidus interna (GPi) are suppressed during urination in patients with PD.

What is known and what this paper adds

Lower urinary tract symptoms are common in PD. Beta oscillations are associated with PD-related motor symptoms, and this study shows that they are also associated with PD-related urinary symptoms.

Participants and setting

This study analyzed data for 10 patients with PD who underwent deep brain stimulation (DBS) of the GPi (n = 5; 1 woman; mean age, 56 years; 9 nuclei) or the subthalamic nucleus (STN; n = 5; 3 women; mean age, 58 years; 8 nuclei) at the John Radcliffe Hospital in Oxford between November 2014 and November 2015.

Design, size, and duration

The participants attended the experiments with full bladders while "on" PD medications. Testing occurred 3–6 days after DBS electrode implantation. The study collected ≥2 separate local field potential (LFP) recordings during 30-second quiet rest periods and then collected LFP recordings during ≤10-second urination periods. Power spectral density analysis was used to isolate beta band (12–25 Hz) signals. The participants completed International Consultation on Incontinence (ICIQ) questionnaires on their urinary tract symptoms.

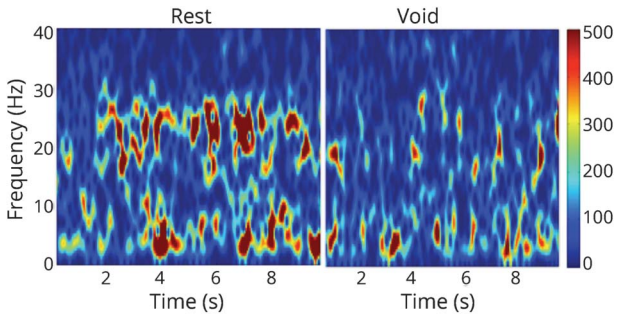
Primary outcomes

The primary outcome was the difference in beta power between the at-rest and during-urination recordings.

Main results and the role of chance

GPi beta power was lower during urination than during rest ($p = 0.011$), but STN beta power was not. Greater GPi beta power suppression was associated with greater incontinence scores ($p = 0.005$) and urination frequency scores ($p = 0.014$) on the ICIQ.

Figure LFP power spectrum in a single participant during rest and urination



Bias, confounding, and other reasons for caution

Another 3 participants were recruited but were excluded because they could not urinate during the experiments. Participants were asked to cease urination after 10 seconds, which is not typical behavior.

Generalizability to other populations

Further studies are necessary to establish the generalizability to other DBS-treated conditions such as dystonia or Tourette syndrome.

Study funding/potential competing interests

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A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.

