33. Tinkhauser G, Pogosyan A, Debove I, et al. Directional local field potentials: a tool to optimize deep brain stimulation. Mov Disord 2017;137(Pt 7):2015–2016.

34. Zaidel A, Spivak A, Grieb B, Bergman H, Israel Z. Subthalamic span of beta oscillations predicts deep brain stimulation efficacy for patients with Parkinson's disease. Brain 2010;133:2007–2021.

Supporting Data

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Pallidal Low-Frequency Activity in Dystonia After Cessation of Long-Term Deep Brain Stimulation

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ABSTRACT: Objective: This study investigates the association between pallidal low-frequency activity and motor sign severity in dystonia after chronic deep brain stimulation for several months.

Methods: Local field potentials were recorded in 9 dystonia patients at 5 timepoints (T1–T5) during an OFF-stimulation period of 5 to 7 hours in parallel with clinical assessment using Burke-Fahn-Marsden Dystonia Rating Scale. A linear mixed effects model was used to investigate the potential association of motor signs with local field potential activity in the low frequency (3–12 Hz) and beta range (13–30 Hz).

Results: A significant association of Burke-Fahn-Marsden Dystonia Rating Scale scores with low-frequency activity (3–12 Hz; b = 4.4; standard error = 1.5, degrees of freedom = 43, $P = 0.006$, 95% confidence interval, 1.3–7.5), but not beta activity (13–30 Hz) was revealed within participants across timepoints.

Conclusion: Low-frequency activity is associated with dystonic motor sign severity, even months after chronic deep brain stimulation. Our findings corroborate the pathophysiological role of low-frequency activity in dystonia and highlight the potential utility as a biomarker for adaptive neuromodulation. © 2019 Charité. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: basal ganglia; deep brain stimulation; dystonia; globus pallidus; local field potentials

Dystonia is defined as "a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both."[1] Deep brain stimulation (DBS) is an effective treatment option for medically refractory dystonia.[2-5] Modulation of network activity by pallidal DBS may restore abnormal cortico-subcortical neuronal communication. The exact mechanism of DBS in dystonia, however, remains unclear.[6] One hypothesis poses that DBS may suppress abnormal oscillatory activity. Indeed, enhanced low-frequency oscillatory activity has been recorded from the basal ganglia of dystonia patients[7-10] that drives and is coherent with dystonic, especially rhythmic, muscle activity.[8,11-13]

We have recently shown that pallidal low-frequency activity, but not beta band activity, (that is also present in dystonia[14]) correlates with the severity of dystonic motor signs, and patients with electrode position close to the maximum low-frequency local field potential (LFP) peak within the pallidum had the best motor outcome with chronic stimulation.[15] Moreover, DBS could suppress low-frequency activity in the short term in patients with predominant phasic, but not tonic, dystonic movements.[16] However, in dystonia the main clinical effect manifests

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Funding agencies: German Research Council Grant KFO247.

Relevant conflicts of interests/financial disclosures: U.S. Received travel grants and seminar fees from Boston and Abbott. A.S. received travel grants from Medtronic. J.K.K. is a consultant to Medtronic and receives fees for consulting from Medtronic and Boston. G.-H.S. has received honoraria from Medtronic and Boston Scientific. P.K. received speaker's fees from Medtronic. A.A.K. has received honoraria and travel grants from Medtronic, Abbott, and Boston Scientific and is a member of the advisory board of Boston Scientific. R.L., B.C.M.v.W., D.K., W.-J.N. have nothing to report.

[Correction added 12 December 2020. The copyright changed after initial online publication.]

Received: 14 May 2019; **Revised:** 5 August 2019; **Accepted:** 5 August 2019

Published online 4 September 2019 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.27838

during a much longer time scale of several weeks or months of continuous stimulation, which has been related to plastic changes and cortico-subcortical reorganization induced by DBS.[17,18] Although pallidal low-frequency activity was previously shown intraoperatively during battery replacement in a single patient,[19] repeated recordings from the pallidum in humans after chronic DBS were not feasible until recently.

Here, we recorded LFPs from the internal segment of the globus pallidus (GPi) after long-term DBS in 9 dystonia patients via an implanted sensing enabled pulse generator (Medtronic Activa PC + S, Minneapolis, Minnesota, USA) to evaluate the occurrence of low-frequency oscillations and their association with dystonic motor signs in pallidal activity after long-term DBS.

Methods

Patients

A total of 9 patients suffering from isolated dystonia and 1 from complex dystonia received DBS using a Medtronic Activa PC + S pulse generator. All patients with isolated dystonia were included in the study (8 women, 1 man, mean age 55.9 ± 11.2 years; Table 1). The Activa PC + S enables postimplantation LFP recording, saving data temporarily on the implantable pulse generator (IPG) and transferring them via telemetry to a tablet.[20,21] The study was approved by the local ethics committees in agreement with the Declaration of Helsinki, and written informed consent was obtained from all patients before surgery. DBS electrodes were implanted bilaterally in the posteroventral–lateral GPi according to standard procedures using preoperative magnetic resonance imaging target planning, intraoperative microelectrode recordings, and test stimulation. Implanted electrodes were localized based on the coregistration of preoperative magnetic resonance imaging and postoperative computed tomography scans and warping to standard Montreal neurological imaging (MNI) space using the extended pipeline of the Lead-DBS toolbox,[22] except for patient 8, whose imaging data were not available.

Recordings

The LFP rest recordings took place at 18.9 ± 13.9 months after surgery (mean ± standard deviation, range 6 to 51 months; Table 1), when patients experienced a clinically meaningful and stable effect of DBS using the sensing-enabled Medtronic Activa PC + S system.

All recordings were performed with medication unchanged (Table 1). Recordings were conducted at the following 5 timepoints: directly after switching off stimulation (T1), after 30 minutes (T2), after 1 hour (T3), after 2 hours (T4), and after 5 to 7 hours (T5). Recordings ON stimulation were obviated because of the DBS-induced strong subharmonic artefacts in the low-frequency range arising while stimulating and recording with the present device, which allowed for bipolar recordings of 1 single contact pair in both hemispheres simultaneously. We therefore obtained recordings for each of the 3 contact pairs in a subsequent fashion for 2 minutes each. Signals were bandpass filtered between 0.5 and 100 Hz, amplified (×2000), and sampled at a rate of 800 Hz. Clinical motor signs were videotaped before recordings with DBS ON (T0) and directly after each recording (T1–T5) and rated by author U.S. offline in a randomized blinded order using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS).

Analysis

The LFP data were inspected for artefacts and analyzed offline using custom MATLAB code (The Mathworks, Natick, MA) partly based on FieldTrip[23] (Donders Center for Cognitive Neuroimaging, University Nijmegen, Nijmegen, the Netherlands; http://fieldtrip.fcdonders.nl/; see Supporting Information for artefact removal). Time series were transformed to the frequency domain using Morlet wavelets with 10-cycle lengths and a frequency resolution of 1 Hz. The resulting power spectra were normalized through division by the standard deviation of power values across the full spectrum, excluding frequency ranges prone to artefacts and visually inspected for oscillatory peaks. To avoid a selection bias and to compare low-frequency versus beta-frequency ranges, we averaged 3 to 12 Hz and 13 to 30 Hz power over all contact pairs and the 2 hemispheres.[24]

Statistics

BFMDRS scores were tested for a significant difference between the first and last timepoints T0 vs. T5 across patients using permutation tests. Therefore, condition (timepoint) affiliations were randomly shuffled 10,000 times to determine the null distribution by flipping the sign of the difference between conditions.

Subsequently, a linear mixed effects regression model was implemented to assess the relationship between low-frequency power and BFMDRS scores within patients while considering repeated measures (recording timepoints) per patient. Maximum likelihood was used as the estimation method. BFMDRS was set as the dependent variable, and low-frequency power (averaged over contact pairs) measured repeatedly within a participant at T1 to T5 as a fixed effect. The intercept was considered as random factor as well as the interaction of patientand low-frequency power as nested random slope factor. To assess variance explained by the full model (fixed and random effects), we report the coefficient of multiple determination $R^2_{\text{conditional}}$. In addition, marginal R^2 was calculated, which is only concerned with the variance explained by the fixed effect.[25] The local effect size Cohen's f^2 is given, which has been proposed for hierarchical and repeated-measure data,[26] for our fixed effect using $R^2_{\text{conditional}}$ from the full model and $R^2_{\text{conditional}}$ from a null model without the fixed effect.[26]

TABLE 1. Clinical details of the patients

#	Age, y	Sex	Diagnosis	Disease duration, y	Time between surgery and recording, mo	Surgical center	DBS electrodes (Medtronic)	Stimulation parameters	Medication	BFMDRS preoperative	BFMDRSSTIM ONT0	BFMDRSSTIM OFFT1	BFMDRSSTIM OFFT5	BFMDRST5–T0 (absolute values)	BFMDRST5–T1(absolute values)
1	33	F	Generalized dystonia	9	51	Berlin	3389	130 Hz, 90 μs GPi right: C 1-, 2.5 V GPi left: C 9-, 3.4 V	None	14	14.5	14.5	22.5	8	8
2	67	F	Segmental dystonia	22	32	Berlin	3389	140 HZ, 90 μsGPi right: C 0-, 2.4 VGPi left: C 9-, 2.3 V	Lorazepam 0.5 mg 1x/d	26	7	10.5	29	22	18.5
3	63	M	Segmental dystonia	24	25	Berlin	3389	140 Hz, 90 μsGPi right: C 1-, 3.3 VGPi left: C 9-, 3.4 V	Clonazepam 0.5 mg 2x/d	22.5	9.5	9.5	21	11.5	11.5
4	63	F	Cervical dystonia	33	15	Berlin	3389	130 Hz, 90 μsGPi right: C 0-, 1.2 VGPi left: C 8-, 1.2 V	Propranolol 40 mg 2x/d	10	5	9	13	8	4
5	52	F	Generalized dystonia	31	9	Berlin	3389	130 Hz, 9 0μsGPi right: C 3-, 3.0 VGPi left: C 11-, 3. 0V	Pregabalin 150 mg 2x/d, Levodopa 200 mg 1x/d	23	15	19	18.5	3.5	-0.5
6	50	M	Multisegmental tardive dystonia	7	6	Berlin	3389	210 Hz, 60 μsGPi right:C 1/C 2-, 1.6 VGPi left: C 9/10-, 1.6 V	Trihexyphenidyl 1 mg 3x/d, Tetrabenazin 12.5 mg 4x/d, Quetiapin 25 mg 2x/d + 75 mg1x/d, Mirtazapin 30 mg,	40	13	11	36	23	25
7	44	F	Generalized dystonia	5	15	Berlin	3389	190 Hz, 90 μs GPi right: C 2/3-, 2.6 V GPi left: C 10/11-, 2.6 V	Trihexyphenidyl 5 mg 3x/d, Clonazepam 0.5 mg 3x/d	17	8	11	23	15	12
8	65	F	Cervical dystonia	23	8	Hannover	3387	210 μs, 130 HzGPi right: C 2-, 3.7 VGPi left: C 10-, 3.7 V	Botox >3 months ago	6	1.5	3	6	4.5	3
9	66	F	Segmental dystonia	9	9	Hannover	3387	130 Hz, 210 μs GPi right: C 0- C2+, 3.0 V GPi left: C 8- C10+, 3. 3V	None	23	8.5	11	17.5	9	6.5
Mean	55.9			18.1	18.9					20.2	9.1	10.9	20.7	11.6	9.8
SD	11.2			10.1	13.9					9.4	4.2	4.0	8.2	6.7	7.6

A total of 9 patients with isolated dystonia who underwent DBS with the Medtronic-PC + S were included in the current study. Age and disease duration are given at time of recording. Stimulation parameters of current DBS settings are listed for each hemisphere. C indicating the active contact and +/- the current flow. If not indicated differently, monopolar stimulation setting is used with the implantable pulse generator (IPG) case serving as anode. Medtronic DBS electrodes were either model 3389 (cases 1–7) or 3387 (cases 8–9), with 4 platinum-iridium cylindrical surfaces (1.27 mm diameter and 1.5 mm length) and a contact-to-contact separation of 0.5 mm (3389) or 1 mm (3387). BFMDRS scores were assessed at baseline preoperatively, before local field potential recordings with DBS-ON (T0) as well as for each recording timepoint T1 to T5 (only T1 and T5 shown). After 5 to 7 hours OFF DBS (T5), 5 of 9 patients reached or exceeded their preoperative baseline BFMDRS score. The differences in BFMDRS scores between T0/T1 versus T5 are shown in absolute values.

DBS, deep brain stimulation; BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; STIM, stimulation; T0, timepoint 0; T1, timepoint 1; T5, timepoint 5; GPi, internal segment of the globuls pallidus; C, contact pair; SD, standard deviation.

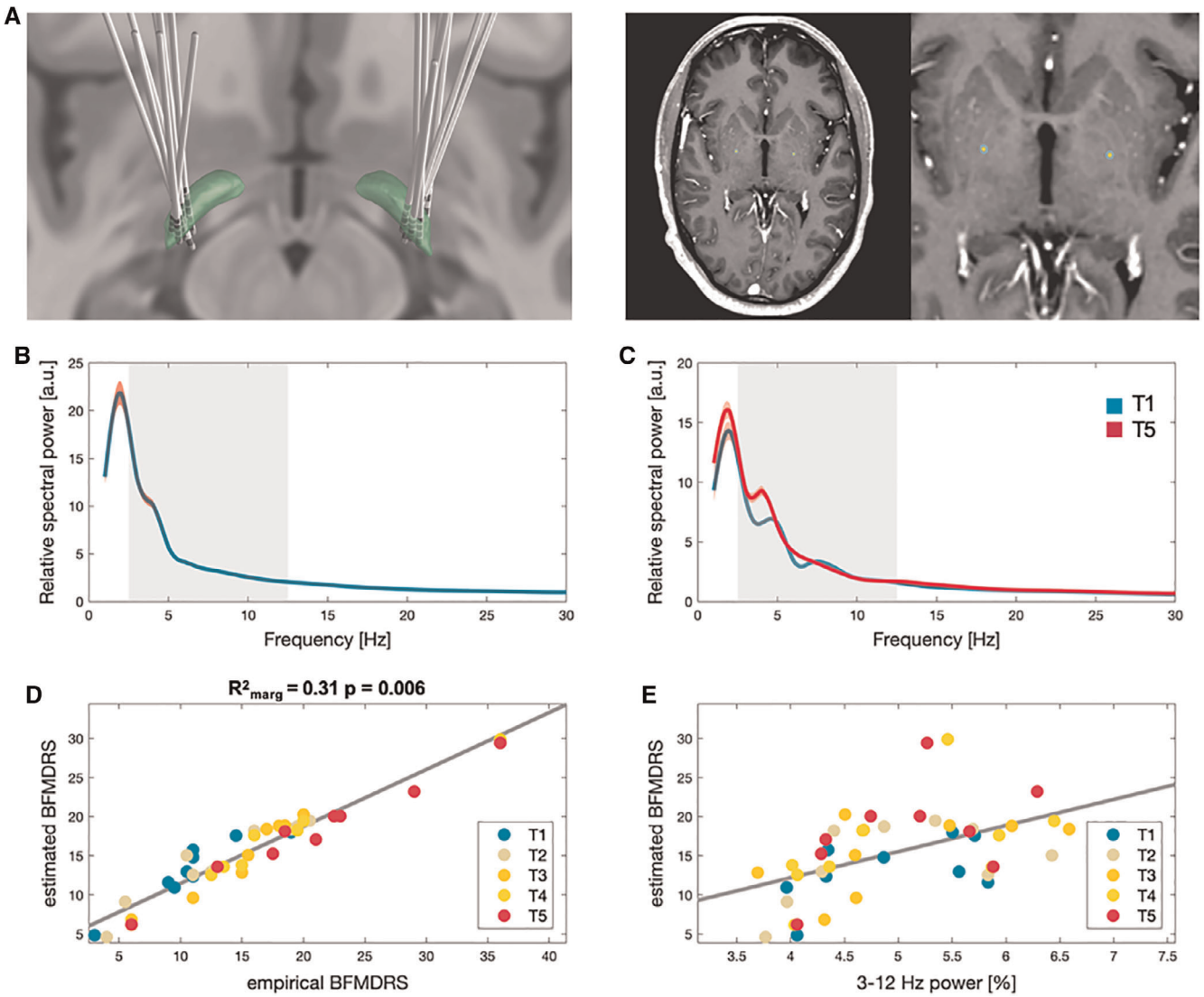

FIG. 1. (**A**) Deep brain stimulation electrode reconstruction showed 11 of 18 deep brain stimulation electrodes placed with at least 3 contacts and another 3 electrodes with at least 2 contacts in the internal segment of the globuls pallidus (internal segment of the globuls pallidus shown in green projected onto montreal neurological imaging (MNI) standard space, DISTAL8 atlas, axial view: slightly below AC–PC plane). Only 1 electrode was placed laterally to the internal segment of the globuls pallidus (subject 9). Right images present an axial magnetic resonance image at the anterior commisure – posterior commisure (AC–PC) plane with lead location by computed tomography–magnetic resonance imaging fusion in subject 6 (whole magnetic resonance imaging and zoomed basal ganglia; leads marked green). (**B**) Power spectrum averaged over contact pairs, hemispheres, timepoints, and patients. SE illustrated in red. (**C**) Individual power spectrum averaged over contact pairs and hemispheres (subject 3, T1 and T5). (**D**) Linear mixed model predicting BFMDRS scores according to correlation between low-frequency power and empirical BFMDRS scores. Timepoints depicted in different colors. (**E**) Low-frequency power depicted against BFMDRS scores estimated by the linear mixed effects model. Timepoints shown in different colors. BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; T0, timepoint 0; T1, timepoint 1; T2, timepoint 2; T3, timepoint 3; T4, timepoint 4; T5, timepoint 5. [Color figure can be viewed at wileyonlinelibrary.com]

Results

All patients showed a recurrence of dystonic motor signs after the cession of DBS. Mean BFMDRS scores changed from 9.1 ± 4.2 at T0 to 20.7 ± 8.2 at T5 ($P = 0.003$; Table 1). Reconstruction of the electrode position confirmed correct placement with at least 1 contact in the GPi in all but 1 electrode (Fig. 1A). Power spectra averaged over all available contact pairs, hemispheres, timepoints, and patients are presented in Figure 1B.

A local maximum in the 3 to 12 Hz low-frequency range was found for every patient in at least 1 contact pair of each timepoint, with a mean of 18.7 ± 6.9 recordings per patient (range 7–30 of 30). Overall, 3 to 12 Hz peaks occurred in 168 of 240 analyzed individual recordings. Beta peaks (13–30 Hz) could be detected in every patient, but not at all timepoints (range 2–16 of 30 recordings per patient), adding up to a total of 94 of 240 analyzed recordings, with overall lower amplitude. No other distinct peaks were revealed in higher frequency bands.

The linear mixed effects regression model revealed a significant association of low-frequency activity with BFMDRS scores within individual patients (b = 4.4, SE = 1.5, degrees of freedom (DF) = 43, $P = 0.006$, 95% confidence interval, 1.3–7.5). Low-frequency activity explained 31% of the variance in BFMDRS in the patients, and the effect was characterized as medium[26] by Cohen's f^2 ($R^2_{\text{marginal}} = 0.31$, $f^2 = 0.26$, $R^2_{\text{conditional}} = 0.82$; Fig. 1D).

Discussion

In the present study, we demonstrate that pallidal low-frequency activity is present and significantly correlated with dystonic motor sign severity after months of chronic DBS in patients with dystonia. Our findings extend previous reports of neurophysiological fingerprints of dystonia after chronic pallidal DBS by showing a direct association of pallidal low-frequency activity with BFMDRS scores within participants when measuring repeatedly up to 7 hours after the cessation of stimulation. This correlation was frequency specific to low frequency, but not beta band, and replicates previous work reporting an association between pallidal low-frequency power and motor sign severity in patients with cervical dystonia.[15]

In Parkinson's disease, beta activity in the basal ganglia has been shown to: 1) be reduced by dopaminergic medication and DBS, 2) correlate with motor sign severity and 3) be preserved after long-term stimulation.[20,27] Because of this modulation and stability over time, recent studies used beta activity as a feedback signal for demand-dependent, adaptive closed-loop stimulation and have already achieved promising preliminary results.[28] Similarly, it has been suggested that pallidal low-frequency activity may contribute to motor circuit dysfunction, resulting in involuntary motor output in dystonia patients and thus may be utilized as a biomarker signal for feedback-based adaptive DBS paradigms,[15] as recently described in a pilot case by Piña-Fuentes and colleagues.[19] Our work provides further evidence in favor of this approach. First, the correlation between low-frequency activity and dystonic motor signs seems to be robust after long-term DBS. Second, our data suggest that this correlation may be present in different forms of isolated dystonia ranging from general, segmental, to cervical dystonia. However, the latter aspect should be verified in larger cohort studies to identify potential differences between dystonia subtypes and specific medication effects on both beta and low-frequency activity as subgroup analyses were not feasible because of the small sample size in the present study. Importantly, our findings should be considered in the context of additional mechanisms such as delayed long-term DBS-induced plastic changes[17,18,29] and electrophysiological changes on the cortical level, where DBS-reduced higher cortical alpha band (8-13Hz) power and coherence[30] and higher pallidal LFP alpha power was associated with increased cortico-pallidal coherence.[31] Finally, there is evidence for a disruption of structural[32] and functional connectivity[33] with the cerebellum that extends the complexity of unified framework for the pathogenesis of dystonic symptoms.

Conclusion

Our results corroborate previous evidence for an association of pallidal low-frequency activity with dystonic motor sign severity even months after chronic DBS. Our findings suggest that low-frequency activity may represent a stable biomarker over time for chronic use as a feedback signal for adaptive stimulation in dystonia. Further research is needed to disentangle the specific role of synchronized oscillatory activity and long-lasting plastic changes and their interaction within the cortico–basal ganglia network for the development and alleviation of motor impairment in dystonia.

Acknowledgment: This study was funded by the German Research Foundation Deutsche Forschungsgemeinschaft (Grant KFO247). Medtronic provided the PC + S pulse generators for this study. We thank Gaetano Leogrande from Medtronic for technical advice on the local field potential recordings. Open access funding enabled and organized by Projekt DEAL.

References

1. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord 2013;28(7):863–873. https://doi.org/10.1002/mds.25475
2. Kühn AA, Volkmann J. Innovations in deep brain stimulation methodology. Mov Disord 2017;32(1):11–19.
3. Volkmann J, Mueller J, Deuschl G, et al. Pallidal neurostimulation in patients with medication-refractory cervical dystonia: a randomised, sham-controlled trial. Lancet Neurol 2014;13(9):875–884. https://doi.org/10.1016/S1474-4422(14)70143-7
4. Vidailhet M, Jutras M-F, Grabli D, Roze E. Deep brain stimulation for dystonia. J Neurol Neurosurg Psychiatry 2013;84(9):1029–1042. https://doi.org/10.1136/jnnp-2011-301714
5. Moro E, LeReun C, Krauss JK, et al. Efficacy of pallidal stimulation in isolated dystonia: a systematic review and meta-analysis. Eur J Neurol 2017;24(4):552–560. https://doi.org/10.1111/ene.13255
6. McIntyre CC, Hahn PJ. Network perspectives on the mechanisms of deep brain stimulation. Neurobiol Dis 2010;38(3):329–337. https://doi.org/10.1016/j.nbd.2009.09.022
7. Silberstein P, Kühn AA, Kupsch A, et al. Patterning of globus pallidus local field potentials differs between Parkinson's disease and dystonia. Brain 2003;126(12):2597–2608. https://doi.org/10.1093/brain/awg267
8. Liu X, Wang S, Yianni J, et al. The sensory and motor representation of synchronized oscillations in the globus pallidus in patients with primary dystonia. Brain 2008;131(Pt 6):1562–1573. https://doi.org/10.1093/brain/awn083
9. Neumann WJ, Huebl J, Brucke C, et al. Enhanced low-frequency oscillatory activity of the subthalamic nucleus in a patient with dystonia. Mov Disord 2012;27(8):1063–1066. https://doi.org/10.1002/mds.25078
10. Wang DD, de Hemptinne C, Miocinovic S, et al. Pallidal deep-brain stimulation disrupts pallidal beta oscillations and coherence with primary motor cortex in Parkinson's disease. J Neurosci 2018;38(19):4556–4568. https://doi.org/10.1523/JNEUROSCI.0431-18.2018
11. Sharott A, Grosse P, Kuhn AA, et al. Is the synchronization between pallidal and muscle activity in primary dystonia due to peripheral

afferance or a motor drive? Brain 2008;131(2):473–484. https://doi.org/10.1093/brain/awm324

12. Chen CC, Kühn AA, Hoffmann KT, et al. Oscillatory pallidal local field potential activity correlates with involuntary EMG in dystonia. Neurology 2006;66(3):418–420. https://doi.org/10.1212/01.wnl.0000196470.00165.7d
13. Liu X, Yianni J, Wang S, Bain PG, Stein JF, Aziz TZ. Different mechanisms may generate sustained hypertonic and rhythmic bursting muscle activity in idiopathic dystonia. Exp Neurol 2006;198(1):204–213. https://doi.org/10.1016/J.EXPNEUROL.2005.11.018
14. Wang DD, de Hemptinne C, Miocinovic S, et al. Subthalamic local field potentials in Parkinson's disease and isolated dystonia: an evaluation of potential biomarkers. Neurobiol Dis 2016;89:213–222. https://doi.org/10.1016/j.nbd.2016.02.015
15. Neumann W-J, Horn A, Ewert S, et al. A localized pallidal physiomarker in cervical dystonia. Ann Neurol 2017;82(6):912–924. https://doi.org/10.1002/ana.25095
16. Barow E, Neumann WJ, Brucke C, et al. Deep brain stimulation suppresses pallidal low frequency activity in patients with phasic dystonic movements. Brain 2014;137(Pt 11):3012–3024. https://doi.org/10.1093/brain/awu258
17. Ruge D, Tisch S, Hariz MI, et al. Deep brain stimulation effects in dystonia: time course of electrophysiological changes in early treatment. Mov Disord 2011;26(10):1913–1921. https://doi.org/10.1002/mds.23731
18. Quartarone A, Hallett M. Emerging concepts in the physiological basis of dystonia. Mov Disord 2013;28(7):958–967. https://doi.org/10.1002/mds.25532
19. Piña-Fuentes D, van Zijl JC, van Dijk JMC, et al. The characteristics of pallidal low-frequency and beta bursts could help implementing adaptive brain stimulation in the parkinsonian and dystonic internal globus pallidus. Neurobiol Dis 2019;121:47–57. https://doi.org/10.1016/j.nbd.2018.09.014
20. Neumann W-J, Staub-Bartelt F, Horn A, et al. Long term correlation of subthalamic beta band activity with motor impairment in patients with Parkinson's disease. Clin Neurophysiol 2017;128(11):2286–2291. https://doi.org/10.1016/j.clinph.2017.08.028
21. Trager MH, Koop MM, Velisar A, et al. Subthalamic beta oscillations are attenuated after withdrawal of chronic high frequency neurostimulation in Parkinson's disease. Neurobiol Dis 2016;96:22–30. https://doi.org/10.1016/j.nbd.2016.08.003
22. Horn A, Li N, Dembek TA, et al. Lead-DBS v2: towards a comprehensive pipeline for deep brain stimulation imaging. Neuroimage 2018;184:293–316. https://doi.org/10.1016/j.neuroimage.2018.08.068
23. Oostenveld R, Fries P, Maris E, Schoffelen J-M. FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011;2011:156869. https://doi.org/10.1155/2011/156869
24. Neumann WJ, Huebl J, Brücke C, et al. Pallidal and thalamic neural oscillatory patterns in Tourette's syndrome. Ann Neurol 2018;84(4):505–514. https://doi.org/10.1002/ana.25311
25. Nakagawa S, Schielzeth H. A general and simple method for obtaining R2 from generalized linear mixed-effects models. Methods Ecol Evol 2013;4(2):133–142. https://doi.org/10.1111/j.2041-210x.2012.00261.x
26. Selya AS, Rose JS, Dierker LC, Hedeker D, Mermelstein RJ. A practical guide to calculating Cohen's f 2, a measure of local effect size, from PROC MIXED. Front Psychol 2012;3:111. https://doi.org/10.3389/fpsyg.2012.00111
27. Little S, Brown P. What brain signals are suitable for feedback control of deep brain stimulation in Parkinson's disease? Ann N Y Acad Sci 2012;1265(1):9–24. https://doi.org/10.1111/j.1749-6632.2012.06650.x
28. Meidahl AC, Tinkhauser G, Herz DM, Cagnan H, Debarros J, Brown P. Adaptive deep brain stimulation for movement disorders: the long road to clinical therapy. Mov Disord 2017;32(6):810–819. https://doi.org/10.1002/mds.27022
29. Ruge D, Cif L, Limousin P, et al. Shaping reversibility? Long-term deep brain stimulation in dystonia: the relationship between effects on electrophysiology and clinical symptoms. Brain 2011;134(Pt 7):2106–2115. https://doi.org/10.1093/brain/awr122
30. Miocinovic S, Miller A, Swann NC, Ostrem JL, Starr PA. Chronic deep brain stimulation normalizes scalp EEG activity in isolated dystonia. Clin Neurophysiol 2018;129(2):368–376. https://doi.org/10.1016/J.CLINPH.2017.11.011
31. Yokochi F, Kato K, Iwamuro H, et al. Resting-state pallidal-cortical oscillatory couplings in patients with predominant phasic and tonic dystonia. Front Neurol 2018;9:375. https://doi.org/10.3389/fneur.2018.00375
32. Argyelan M, Carbon M, Niethammer M, et al. Cerebellothalamocortical connectivity regulates penetrance in dystonia. J Neurosci 2009;29(31):9740–9747. https://doi.org/10.1523/JNEUROSCI.2300-09.2009
33. Neumann WJ, Jha A, Bock A, et al. Cortico-pallidal oscillatory connectivity in patients with dystonia. Brain 2015;138(Pt 7):1894–1906. https://doi.org/10.1093/brain/awv109

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Peripheral Blood Inflammatory Cytokines in Idiopathic REM Sleep Behavior Disorder

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Funding agencies: This work was supported by grant No. 04-2018-0550 (2018-1265) from the SNUH Research Fund and the National Research Foundation of Korea (NRF) grant funded by the Minister of Science, ICT and Future Planning (No. NRF-2014R1A2A2A04003858; 2017M3C7A1029485; 2017R1A2B2012280).

Relevant conflicts of interest/financial disclosures: Nothing to report.

Full financial disclosures and author roles may be found in the online version of this article.

Received: 20 May 2019; **Revised:** 28 July 2019; **Accepted:** 4 August 2019

Published online 30 September 2019 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.27841