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BRIEF COMMUNICATION

Effect of pallidal deep-brain stimulation on articulation rate in dystonia

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Abstract
Pallidal deep-brain stimulation of the internal globus pallidus (GPi-DBS) is an effective treatment for dystonia. However, GPi-DBS may cause important stimulation-induced side effects such as hypokinetic dysarthria, which is particularly manifested by articulation rate abnormalities. However, little data regarding the effect of the location of the electrode and stimulation parameters for pallidal stimulation on articulation rate in dystonia is available. Speech data were acquired from 18 dystonic patients with GPi-DBS and 18 matched healthy controls. Each of dystonic patients was tested twice within 1 day in both the GPi-DBS ON and GPi-DBS OFF stimulation conditions. Compared to healthy controls, the decreased diadochokinetic rate and slower articulation rate in dystonic patients were observed in both stimulation conditions. No significant differences in speech rate measures between stimulation conditions were detected with no relation to contact localization and stimulation intensity. Our findings do not support the use articulation rate as a surrogate marker of stimulation-induced changes to the speech apparatus in dystonia.

Keywords Dystonia · Deep-brain stimulation · Pallidal · Dysarthria · Speech · Acoustic analysis

Introduction

Although articulation rate abnormalities are frequent stimulation-induced side effects of deep-brain stimulation (DBS) of the internal globus pallidus (GPi), the reasons behind the occurrence of these side effects are not yet well explored. Increased articulation rate was the only significant change observed in the longitudinal assessment of 25 dystonic patients before and 12 months later after GPi-DBS surgery [1]. Similarly, increased articulation rate in the GPi-DBS ON when compared to GPi-DBS OFF stimulation condition was the only change revealed in the group level in 15 patients with primary dystonia [2]. Contrary, a recent study reported slowing of speech as a stimulation-induced side effect in 10 dystonic patients with GPi-DBS associated with more posteriorly located active lead contacts [3]. Therefore, particular questions of interest are whether to apply the articulation rate in dystonia as a potential marker of GPi-DBS-induced hypokinetic dysarthria and whether it is associated with the position of the active electrode contact or with the stimulation parameters.

Patients and methods

We examined 18 patients (12 women, 6 men), mean age 49 (± standard deviation 18) years, with dystonia of various origins (12 idiopathic with isolated dystonia, 2 idiopathic with parkinsonism, 2 DYT-1, 1 PINK1, 1 post-anoxic) and distributions (10 generalized and 8 cervical) treated with GPi-DBS bilaterally (Table 1). In addition, the healthy control group consisted of 18 sex- and age-matched subjects (12 women, 6 men; mean age 49 ± 18 years) with no history of neurological or communication disorders.

Each dystonic patient was tested in two conditions within the same day: in the DBS chronically switched ON and 2 hours later after switching the DBS OFF. All patients were implanted bilaterally with a quadripolar electrode to the posteroventrolateral portion of the GPi. The position of the active electrode was measured using a 1.5-T T1-weighted magnetization-prepared rapid acquisition gradient echo sequence (resolution of $1 \times 1 \times 1$ mm^3) acquired 3.2 (± 2.0) years after implantation. The intensity of stimulation (mean

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Table 1 Clinical characteristics of dystonia patients with bilateral GPi-DBS

Clinical characteristics						Speech characteristics				Electrode position (native/adjusted)			Intensity
			Disease	GPi-DBS		Diadochokinetic rate		Articulation rate		*x*	*y*	*z*	
Code	Gender	Age (years)	Duration (years)	Duration (years)	Type	GPi-DBS OFF (syll/s)	GPi-DBS ON (syll/s)	GPi-DBS OFF (syll/s)	GPi-DBS ON (syll/s)	Coordinate (mm)	Coordinate (mm)	Coordinate (mm)	(mV.s.Hz)
d1	M	74	12	2	Generalized	6.3	5.1	5.6	5.6	17.3/16.0	4.7/4.3	5.2/4.6	145
d2	M	31	11	3	Generalized + parkinsonism	7.6	7.1	5.6	5.0	16.0/13.8	3.7/4.3	3.8/2.9	178
d3	F	40	13	3	Cervical	6.3	6.6	6.1	6.3	16.7/16.5	4.5/3.1	− 0.2/2.0	109
d4	F	63	10	2	Generalized	5.8	5.8	6.0	6.4	15.1/14.3	1.0/2.6	5.8/5.4	63
d5	M	18	10	5	Generalized (DYT1)	7.2	6.5	6.1	6.5	17.8/15.3	6.5/6.1	0/0.2	131
d6	F	54	10	2	Cervical	7.1	7.2	5.7	5.6	17.4/16.2	4.3/4.7	2.0/2.5	42
d7	F	76	12	2	Cervical	5.5	5.4	4.9	5.2	21.1/15.7	4.7/5.2	3.9/2.4	80
d8	F	58	15	7	Cervical	4.0	2.9	3.5	3.2	17.2/15.9	3.3/2.9	0.3/1.8	133
d9	F	52	17	3	Cervical	6.2	6.4	6.4	5.1	17.9/17.9	3.4/3.4	1.4/1.9	108
d10	F	57	9	1	Cervical	6.5	5.8	6.5	6.4	16.1/18.0	7.0/5.7	2.0/1.5	39
d11	M	57	10	4	Cervical	5.6	6.8	5.2	5.4	15.4/16.3	2.9/3.5	4.9/4.4	84
d12	F	44	22	4	Cervical	5.8	6.6	6.2	5.9	15.8/16.1	3.6/2.9	5.8/4.1	103
d13	F	54	27	3	Generalized + parkinsonism (PINK1)	5.2	4.4	5.2	4.9	17.7/17.9	2.5/4.0	2.1/3.0	54
d14	F	43	17	6	Generalized	7.4	7.7	4.6	4.4	14.3/15.7	6.3/3.4	3.5/3.8	316
d15	M	28	16	1	Generalized (postanoxic)	7.3	7.8	6.2	5.3	14.4/14.3	3.5/5.0	3.6/2.8	15
d16	M	16	1	1	Generalized	6.9	6.4	3.0	1.9	15.2/15.9	9.3/6.1	2.9/3.8	110
d17	F	74	8	1	Generalized + parkinsonism	5.5	5.9	6.9	6.9	17.0/15.2	4.6/4.6	2.0/0.3	216
d18	F	36	25	7	Generalized (DYT1)	7.0	7.8	4.8	4.6	15.9/17.5	4.1/4.4	4.3/4.4	135

GPi-DBS ON internal globus pallidus deep-brain stimulation chronically switched ON, *GPi-DBS OFF* internal globus pallidus deep-brain stimulation switched OFF

115 ± 71 mV.s.Hz) was calculated using a previously published formula [4]. The position of the most distal contact was established in the native space focusing on the distal artifact. The *x*-coordinate was measured from the wall of the third ventricle at the level of the midcommissural point (MCP), whereas the *y*- and *z*-coordinates were measured from the MCP according to the previously published method [5]. In addition, the patient's native coordinates were linearly transformed based on group mean values for the *x*-, *y*-, and *z*-coordinates separately to compensate for the main source of anatomical variability. The *x*-coordinate was adjusted to the mean hemispheric width measured from the MCP to the most lateral boundary of the temporal lobe, the *y*-coordinate to the mean length of AC-PC line, and the *z*-coordinate to the mean distance from the MCP to the superficial layer of the brain at the vertex. For the correlation analyses with speech parameters, the native as well as adjusted *x*-, *y*- or *z*-coordinates of the left and right electrode was averaged for each patient (mean native *x* 16.6 ± 1.6 mm; mean native *y* 4.4 ± 1.9 mm; mean native *z* 2.9 ± 1.9 mm; mean adjusted *x* 16.0 ± 1.2 mm; mean adjusted *y* 4.2 ± 1.1 mm; mean adjusted *z* 2.9 ± 1.4 mm).

Speech recordings were performed in a quiet room with a low ambient noise level using a head-mounted condenser microphone (Beyerdynamic Opus 55, Heilbronn, Germany) placed approximately 5 cm from the subject's mouth. Speech signals were sampled at 48 kHz with 16-bit resolution. All participants were instructed to perform /pa/-/ta/-/ka/ diadochokinetic syllable repetition per one breath as fast, steadily, and accurately as possible and to read a short paragraph of standardized text composed of 80 words. Both tasks were repeated two times for every subject per session. The diadochokinetic rate was computed as a number of syllable vocalizations per second [6]. The articulation rate was calculated as the number of syllables per second after removing periods of silence exceeding 60 ms [6]. To provide greater stability of speech assessment, the final values were averaged across two repetitions.

A repeated measure analysis of variance with the post hoc Fisher least squares difference was used to assess group differences (GPi-DBS ON vs. GPi-DBS OFF vs. controls). The Pearson correlation analysis was applied to search for the relationship between speech and clinical data.

Results

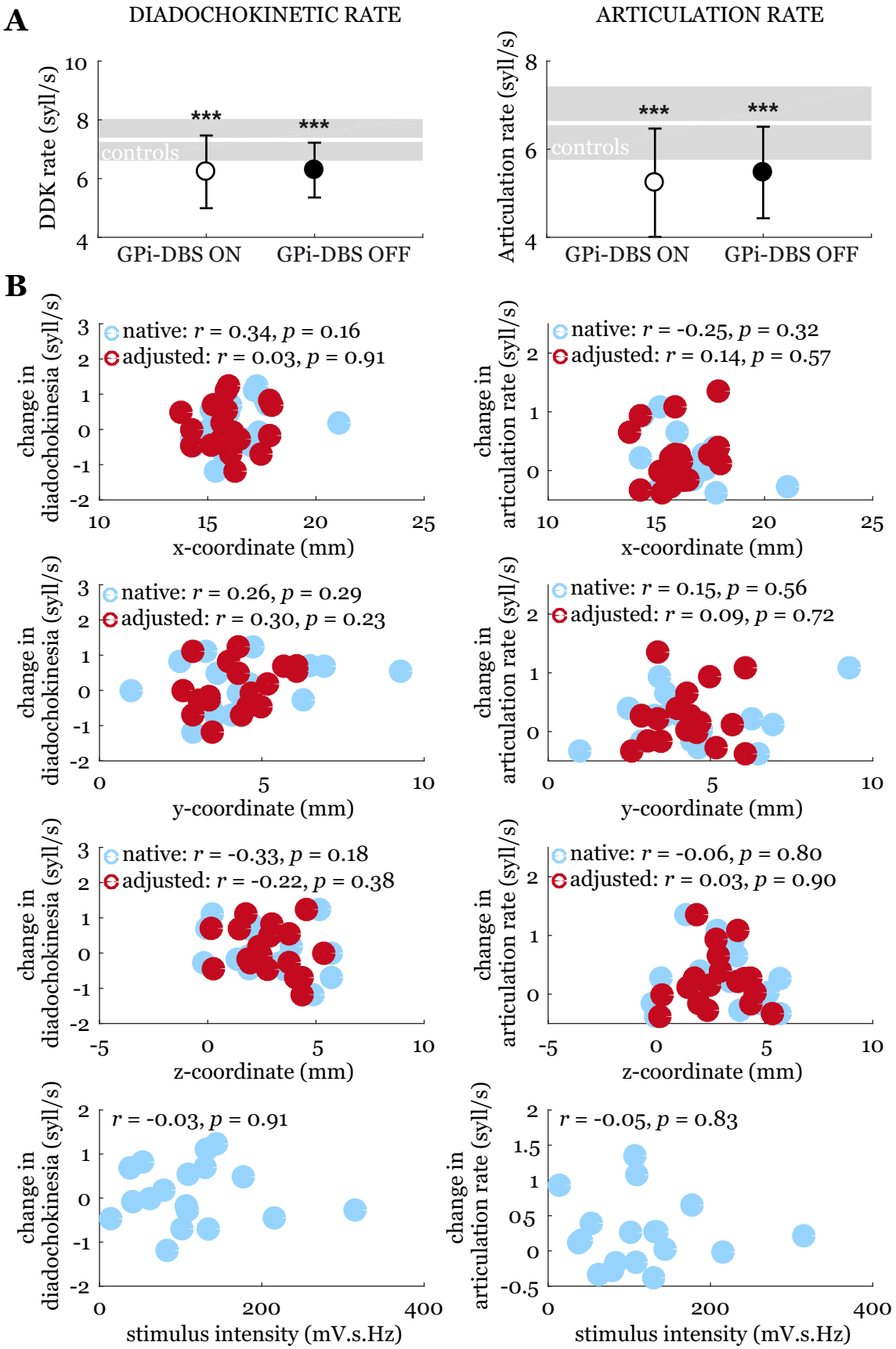
Decreased diadochokinetic rate and slower articulation rate were found between patients in both GPi-DBS ON and GPi-DBS OFF conditions and healthy controls ($p < 0.001$) (Fig. 1a). No differences between GPi-DBS OFF and GPi-DBS ON conditions were detected for diadochokinetic rate ($p = 0.71$) and articulation rate ($p = 0.06$). No correlations between change in speech variables and contact localization (native or adjusted) and stimulus intensity were observed (Fig. 1b).

Discussion

Our findings do not support the use of articulation rate as a surrogate marker of stimulation-induced changes to the speech apparatus in dystonia. In agreement with the expected slower speech due to hyperkinetic dysarthria in dystonia [6, 7], we found a decreased diadochokinetic rate as well as lower articulation rate in our dystonic patients in both stimulation conditions compared with healthy controls. However, we found no significant differences in diadochokinetic rate and articulation rate between GPi-DBS ON and GPi-DBS OFF conditions with no relation to contact localization and stimulation intensity. In particular, based on almost double sample size of 18 dystonic patients, we were unable to reproduce spatial association between GPi-DBS-induced slowing of speech and more posteriorly located active contacts previously described by Pauls et al. [3]. They surprisingly interpreted these findings as signs of hypokinetic dysarthria although parkinsonian speech is typically associated with the opposite—that is with an overall increased rate [1, 2, 7]. In addition, it is not clear whether Pauls et al. [3] used left/right average of the coordinates and how long after surgery the post-implantation CT or X-rays were taken. Methodological issues might be the reason why comparison should be considered with caution because the position of the electrode might be affected by collateral edema or pneumocephalus when the imaging is made few days or weeks after surgery [8]. In our study, the imaging was performed with sufficient delay after the implantation, and therefore the position of the electrode was free of such artifacts.

No relation observed between articulation rate and contact localization should be interpreted with caution as dystonic patients may differ in morphometry and topography of basal ganglia, and that performed adjustment may insufficiently compensate for the majority of individual anatomical differences. Unfortunately, there is no widely accepted way for coordinate normalization within subcortical structures. Common linear [3, 5] and non-linear approaches [9] are widely based on assumptions considering cortical structures or large scale probability maps neglecting small-scale variations at the subcortical level. It should also be noted that the results of our analyses are based on a heterogeneous cohort of dystonic patients with short duration without DBS. Therefore, further research on the homogeneous sample with longitudinal examinations before and after the implantation is warranted.

Switching the GPi-DBS OFF may cause either improvement of the aggregated hypokinetic dysarthria or deterioration of controlled orolingual symptoms related to dystonia [10]. Therefore, the consistent terminology and future research


A
DIADOCHOKINETIC RATE
ARTICULATION RATE
DDK rate (syll/s)
Articulation rate (syll/s)
controls
***
GPi-DBS ON
GPi-DBS OFF
B
change in diadochokinesia (syll/s)
change in articulation rate (syll/s)
native: r = 0.34, p = 0.16
adjusted: r = 0.03, p = 0.91
native: r = -0.25, p = 0.32
adjusted: r = 0.14, p = 0.57
x-coordinate (mm)
native: r = 0.26, p = 0.29
adjusted: r = 0.30, p = 0.23
native: r = 0.15, p = 0.56
adjusted: r = 0.09, p = 0.72
y-coordinate (mm)
native: r = -0.33, p = 0.18
adjusted: r = -0.22, p = 0.38
native: r = -0.06, p = 0.80
adjusted: r = 0.03, p = 0.90
z-coordinate (mm)
r = -0.03, p = 0.91
r = -0.05, p = 0.83
stimulus intensity (mV.s.Hz)

◀ **Fig. 1** **a** Mean values (standard deviations) for dystonia patients in both stimulation conditions (GPi-DBS ON, GPi-DBS OFF) and controls (shaded area) with statistically differences between dystonia and controls at the level $***p < 0.001$. **b** Correlation between change in diadochokinetic rate and articulation rate with the GPi-DBS OFF and GPi-DBS ON conditions and the distance of the both native (blue) and adjusted (red) active contacts of the electrode and stimulus intensity

based on cross-sectional analysis should optimize the selection of measures used for the assessment of GPi-induced hyperkinetic and hypokinetic speech disorders in dystonia patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Each participant provided written, informed consent, and the study was approved by the Ethics Committee of the General University Hospital in Prague, Czech Republic.

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