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Short Communications

Instability of speech in Parkinson disease patients with subthalamic nucleus deep brain stimulation

Short title (running head): Instability of speech in PD with STN-DBS

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ABSTRACT

Introduction: The impact of deep brain stimulation (DBS) on speech rhythm and its mechanism remains unclear. We investigated speech rhythm characteristics of patients with Parkinson's disease (PD) treated with subthalamic nucleus (STN) DBS to understand the underlying pathophysiology better.

Methods: We enrolled a total of 105 participants and evaluated speech rhythm performances among patients with PD who had undergone STN-DBS (the PD-DBS group), patients with PD treated only with medication (the PD-Med group), patients with cerebellar ataxia (the CA group), and healthy controls (the HC group). Each participant was asked to repeat the syllable /pa/ at a comfortable self-chosen steady pace. A widely-used software (the Motor Speech Profile) program performed an acoustic analysis.

Results: Compared to the PD-Med and HC groups, speech rate instability (DDKjit) was significantly higher in the PD-DBS and CA groups ($p < 0.01$). However, after DBS was turned off, the DDKjit of the PD-DBS group improved to a level comparable to that of the PD-Med and HC groups. In contrast to the significantly higher variability of speech volume (DDKcvi) in the CA group, the PD-DBS group showed similar DDKcvi to the PD-Med and HC groups.

Conclusions: STN-DBS affects the speech rate stability of patients with PD. Speech rhythm disorders caused by STN-DBS were phenotypically similar to that in CA in terms of interval variability but different regarding amplitude variability. Further studies are warranted to elucidate the underlying pathophysiology of speech rhythm disorders in PD patients treated with DBS.

Key words: Parkinson's disease, subthalamic nucleus deep brain stimulation, dysarthria, instability of speech, speech rhythm, cerebellar ataxia.

Introduction

Subthalamic nucleus deep brain stimulation (STN-DBS) improves motor fluctuation of patients with advanced Parkinson's disease (PD) but may worsen speech functions [1]. The major speech characteristics in PD patients treated with STN-DBS include, breathy voice, strained voice, imprecise consonants, and hypernasality [2], as well as speech rhythm disturbances, including stuttering [3]. In our previous study, approximately 20% of patients with PD experienced worsened stuttering with STN-DBS ON [2]. Likewise, another study reported that the stability of speech, measured by the variance coefficient of intervals in syllable repetition tasks, was worse with STN-DBS ON [4]. Intriguingly, there was no significant difference in speech rhythm variability between the on- and off-medication states [4]. The authors speculated that considering the unresponsiveness of speech rhythm disorders to dopaminergic medication, alternative circuits such as the cerebellar circuit may be responsible for maintaining the speech rhythm. This hypothesis is consistent with previous earlier reports indicating the relationship between speech disturbances and the current spread of STN-DBS to the cerebellothalamic fibers [5, 6]. However, to the best of our knowledge, no study ever compared speech rhythm characteristics between patients with PD-DBS and those with cerebellar ataxia (CA). Also, the variability of speech volume with DBS ON and OFF has never been assessed.

This study aimed to characterize speech rhythm disturbances (regularity both in intervals and amplitude) in PD patients treated with STN-DBS and better elucidate its underlying pathophysiology. We compared speech rhythm performances among PD patients treated with STN-DBS, PD patients

treated only with medications, and healthy controls (HC). Furthermore, we enrolled CA patients to understand the similarities and differences between speech rhythm disturbances induced by DBS and those in patients with CA.

Materials and methods

Participants

We enrolled four groups of patients: patients with PD who underwent bilateral STN-DBS (the PD-DBS group), patients with PD treated only with medication (the PD-Med group), patients with CA (the CA group), and HC (the HC group). The inclusion criteria for PD patients were as follows: 1) diagnosis of PD according to the United Kingdom Parkinson's Disease Society brain bank criteria, 2) absence of other neurological diseases, 3) having Japanese as a native language, and 4) the absence of severe cognitive impairment or neuropsychiatric disorders, including ataxia, that might hinder speech assessment. Regarding PD-DBS patients, the following additional inclusion criteria were applied: 1) bilateral STN implantation at the Nagoya University Hospital, 2) postoperative assessments after at least 6 months, and 3) agreement to undergo on- and off-stimulation assessments. The inclusion criteria for the CA group were as follows: 1) the presence of slowly-progressive CA without other types of motor manifestations such as parkinsonism and spasticity, 2) the absence of dementia fulfilling the DSM-IV criteria and autonomic dysfunctions, 3) the absence of autoimmune or metabolic causes of ataxia, and 4) disease onset after 40 years old. We also enrolled age- and sex-

matched HCs. This study adhered to the Ethics Guidelines for Epidemiological Studies endorsed by the Japanese government. The Ethics Review Committee of the Nagoya University Graduate School of Medicine approved this study, and all participants provided informed consent.

Acoustic Analyses of instability of syllable repetition

All the participants underwent speech analysis using acoustic measurements. All speech samples were recorded in a sound-treated room and digitized in a voice recorder (ICD-SX813; SONY, Tokyo, Japan). A microphone (ECM-MS907; SONY, Tokyo, Japan) was positioned to maintain a constant mouth-to-microphone distance of 15 cm during speech recording. The recorded speech samples were subsequently used for perceptual and acoustic analyses.

The methodology of acoustic analysis was described previously [4, 7]. Briefly, each participant was asked to repeat the syllables /pa/ at a comfortable self-chosen steady pace without accelerating or slowing the articulatory velocity. The instability of syllable repetition was analyzed using the Motor Speech Profile (MSP) programs (Computerized Speech Lab; KayPENTAX, Lincoln Park, NJ). Of the recorded syllable repetition of 25 times and the 5th through the 20th syllables were extracted for the analysis. We used 4 major parameters of the MSP program: the average number of /pa/ per sec. (average diadochokinesis rate, DDKavr); variability of the interval of /pa/ in the whole speech sample (coefficient of variation of the diadochokinesis interval, DDKcvp); variability of /pa/ per interval (perturbations of the diadochokinesis interval, DDKjit); and the variability of speech volume (coefficient

of variation of the diadochokinesis peak intensity, DDKcvi). In addition, the PD-DBS group underwent syllable repetition tasks 30 minutes after stimulation cessation for the on- and off-stimulation comparisons [2, 8]. Note that patients with PD were assessed only in the on-state under continued medication.

Statistical analysis

Clinical backgrounds and acoustic variables were compared among the four groups using the Kruskal–Wallis test and the *post-hoc* Holm test using R (http://www.r-project.org/). The other statistical analyses were performed using the SPSS statistics 26 (IBM, Chicago, IL, USA). PD-specific clinical variables (UPDRS III, IV, and LEDD) were compared between the PD-DBS and PD-Med groups using the Mann–Whitney U test. Acoustic variables were compared between the on- and off-stimulation conditions using the Wilcoxon signed-rank test. P-value < 0.05 were considered statistically significant.

Results

Participants

Twenty-six PD-DBS patients, 44 PD-Med patients, and 24 CA patients met the inclusion criteria. Consequently, a total of 105 participants including 11 HC subjects participated in this study (Table 1, Supplementary Figure 1). The CA group comprised 14 genetically confirmed autosomal-

dominant SCA patients (SCA6, n = 5; SCA31, n = 8; SCA3, n = 1) and 10 without genetic confirmation (6 familial and 4 sporadic cases). Clinically, all the SCA patients showed pure CA with a MRI findings of cerebellar atrophy. There were no significant differences in sex, age, or cognitive function among the groups ($p > 0.05$).

Acoustic parameters in the PD-DBS and other groups.

There were no significant differences in the number of /pa/ per 3 sec between all the groups (DDKavr, $p = 0.604$, Figure 1). DDKjit of the PD-DBS group in the on-stimulation condition and that of the CA group were significantly higher than those of the PD-Med and HC groups. The CA group had significantly higher DDKcvp and higher DDKcvi than the PD-Med and HC groups. The PD-DBS group had significantly lower DDKcvi than the CA group ($p < 0.001$).

Changes of DDK parameters in the DBS on- and off-conditions

DDKjit, a parameter of speech rhythm variability, was the only parameter that showed significant changes after STN-DBS stopped ($p < 0.01$, Figure 2). At an individual level, we observed improvement of DDKjit in 69.2% (18/26) of the PD-DBS patents after stopping STN stimulation (Supplementary Figure 2).

Discussion

We investigated the effects of DBS on speech rhythm performances using syllable repetition analysis. One of the strengths of this study is that we had HCs and patients with CA for comparison. The variability of speech rate (DDKjit) in the PD-DBS and CA groups was significantly perturbed compared to that in the PD-Med and HC groups. In contrast to the high variability of speech volume (DDKcvi) in the CA group, PD-DBS patients showed comparable DDKcvi to those in the PD-Med and the HC groups. Furthermore, DDKjit in the PD-DBS group significantly improved after STN-DBS was turned off. More specifically, both the PD-DBS and CA patients showed increased variability in the speech rate when compared to the HC. In contrast, only the CA patients showed increased variability in speech volume. These results suggest that the speech rhythm disturbances caused by STN-DBS are similar to those in CA in terms of interval variability but differ in amplitude variability.

Although the exact mechanism remains unknown, there seem to be several possible hypotheses of speech rhythm disturbances in PD patients treated with STN-DBS. First, electrical stimulation might interfere with the normal functioning of the BG-thalamo-cortical network, which plays an essential role in maintaining speech rhythm [9]. A recent study suggested that stuttering might be a circuit disorder in the BG-cortex rather than one specific brain region [10]. In our previous prospective study, 16 out of 32 patients with PD were stuttering at baseline, and additional three patients (9%) developed stuttering during the one-year follow-up after bilateral STN implantation [8]. Notably, in a subset of patients (22%), stuttering improved when the stimulation was turned off. This finding is consistent with the results from another cross-sectional study [2]. Similarly, earlier studies and case reports have shown that STN-DBS

or globus pallidus internus (GPi) DBS either induced or aggravated stuttering [10]. These findings suggest that although repetitive speech disorders are primarily caused by PD, they could also emerge after DBS targeting the STN or GPi. Collectively, speech rhythm disturbances may occur when the normal rhythm of speech cannot be produced due to unsatisfactory compensation for the dysfunction of the speech network.

The second possible explanation for speech rhythm variability aggravated by STN-DBS is that electrical stimulation alters the function of the cerebral cortex via the hyperdirect pathway [11]. The cumulative evidence suggests that the hyperdirect pathway may play an important role in motor improvement of PD patients after STN-DBS. Although the roles of the hyperdicrent pathway in adverse effects remain unclear, stimulation of this pathway might affect the maintenance of speech rhythm.

Finally, another potential explanation for speech rhythm disturbances after STN-DBS is the modulation of the cerebellar pathways because current spread into the cerebellothalamic fibers was reported to cause ataxia or speech disturbance [2,5]. Otherwise, direct connections between the cerebellum and the STN could be responsible for these kinds of adverse effects [12]. However, in the present study, STN-DBS did not worsen speech volume variability in PD patients. We cannot exclude the possibility that coexisting hypokinetic speech features were responsible for this observation. Future imaging-based studies should explore possible relationships between speech rhythm disturbances and the current spread to the cerebellothalamic fibers.

This study had several limitations. First, our cohort had a relatively small sample size. Second,

the PD-DBS patients were assessed only in the on-state under continued medication. Although an earlier study reported no significant difference in the speech rhythm variability between the on- and off-medication states [4], the potential impact of medication on speech function cannot be excluded. Third, the assessments were performed first with DBS ON and then with DBS OFF in an unblinded manner. Additionally, the off-stimulation assessments were done relatively shortly after stimulation cessation (30 minutes) for a practical reason. Although past studies found significant changes in speech function with a 30-minute interval, larger changes might have been observed with a longer off-stimulation period [1,2,8]. Finally, we did not analyze electrode positions and volume of tissue activated. Analyzing the relationship between DBS-induced speech rhythm disorders and specific tracts may shed further light on the underlying pathophysiology.

In conclusion, speech rhythm disorders caused by STN-DBS were phenotypically distinct from those in cerebellar disorders. Speech rate stability is affected in patients with PD who underwent STN-DBS and in patients with CA; however, increased variability of speech volume is observed only in CA but not in PD-DBS. Further studies are warranted to elucidate the pathophysiology of speech rhythm disorders in PD patients treated with DBS to identify the clinical outcomes of DBS further.

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Competing interests

The authors declare that there are no conflicts of interest relevant to this work.

Author's contributions

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique. Y.T.: 1(A-C), 2(A-C), 3A. T.T.: 1(A-C), 2(A, C), 3(A, B). H.W.: 1A, 2(A, C), 3(A, B). J.T.: 1(A-C), 3B. D.N. and S.M.: 1(A-C), 2C, 3B. M.S.: 1(A-C), 2(A, C), 3(A, B). K.H.: 1C, 2C, 3(A, B). Y.S., K.Y., and M.H.: 1(A-C), 2(A, C), 3(A, B). K.K. and K.H.: 1C, 3B. M.Y.: 3B. G.S.: 1(B, C), 2C, 3B. M.K.: 1(A-C), 2(A, C), 3(A, B).

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Table

Table 1. Patient characteristics

	PD		CA group	HC group	*P* value *
	PD-DBS group	PD-Med group			
Number	26	44	24	11	-
Sex (female, %)	61.5	56.8	62.5	54.5	-
Age (y)	65.9 ± 8.9	64.7 ± 7.3	60.6 ± 9.5	67.3 ± 11.0	n.s.
Disease duration (y)	13.0 ± 4.1	11.3 ± 4.5	8.4 ± 5.1	n/a	< 0.001
Education (y)	13.7 ± 2.9	13.2 ± 3.2	13.4 ±2.0	15.5 ± 4.4	n.s.
UPDRS-III on	12.2 ± 6.5	14.4 ± 8.6	n/a	n/a	n.s.
UPDRS-IV	3.2 ± 3.1	6.1 ± 3.0	n/a	n/a	0.001
LEDD (mg)	716.7 ± 302.2	911.8 ± 376.1	n/a	n/a	0.006
MMSE	28.2 ± 2.1	28.1 ± 1.9	28.3 ± 1.6	n.d.	n.s.
MoCA-J	25.0 ± 2.7	24.9 ± 2.6	25.3 ± 4.0	26.5 ± 4.0	n.s.
Verbal fluency					
Letter (number/min.)	10.0 ± 4.0	10.9 ± 3.4	9.2 ± 3.6	10.3 ± 4.1	n.s.
Semantic (number/min.)	15.7 ± 5.1	18.0 ± 4.1	16.3 ± 3.5	15.5 ± 4.4	n.s.
Speech intelligibility	2.0 ± 0.5	1.7 ± 0.5	2.0 ± 0.4	n/a	0.024
Speech naturalness	3.1 ± 0.9	2.4 ± 0.8	3.4 ± 0.9	n/a	< 0.001
Postoperative period (m)	25.2 ± 8.2	n/a	n/a	n/a	
STN-DBS conditions					
Left					
Voltage (V)	1.9 ± 0.5	n/a	n/a	n/a	
Frequency (Hz)	133.1 ± 8.7	n/a	n/a	n/a	
Pulse width (μS)	69.2 ± 13.8	n/a	n/a	n/a	
Right					
Voltage (V)	2.0 ± 0.5	n/a	n/a	n/a	
Frequency (Hz)	132.7 ± 9.0	n/a	n/a	n/a	
Pulse width (μS)	68.1 ± 13.3	n/a	n/a	n/a	

Values are mean ± SD. *, Comparisons of two groups were performed using Mann–Whitney U tests, and comparisons of ≥ three groups were performed using Kruskal–Wallis tests with post-hoc Holm tests. *P* value < 0.05 was considered significant; n.s., not significant; n/a, not applicable; n/a, not applicable.

PD, Parkinson Disease; PD-DBS, Parkinson disease patients treated with subthalamic nucleus deep brain stimulation; PD-Med, Parkinson disease patients treated with medical therapy alone; CA, cerebellar ataxia; HC: healthy control; UPDRS-III, Unified Parkinson's Disease Rating Scale motor examination; UPDRS-IV, Unified Parkinson's Disease Rating Scale motor complications; LEDD, levodopa equivalent daily dose; MMSE, Mini-Mental State Examination; MoCA-J, Montreal Cognitive Assessment Japanese version; STN-DBS, subthalamic nucleus deep brain stimulation.

Figure legends

Fig. 1: DDK acoustic parameter of syllable repetition in the PD-DBS group, PD-Med group, CA group and HC group.

† $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$: significant difference within group by post-hoc Holm test.

** $p < 0.01$: DBS on-condition vs. off-condition in PD-DBS group by Wilcoxon signed-rank test.

PD, Parkinson Disease; PD-DBS, Parkinson disease patients treated with subthalamic nucleus deep brain stimulation group; Off, off-stimulation condition; On, on-stimulation condition; PD-Med, Parkinson disease patients treated with medical therapy alone group; CA, cerebellar ataxia group; HC: healthy control group; DDKavr, average diadochokinesis rate; DDKcvp, coefficient of variation of diadochokinesis interval; DDKjit, perturbations of diadochokinesis interval, DDKcvi, coefficient of variation of diadochokinesis peak intensity.

Figure

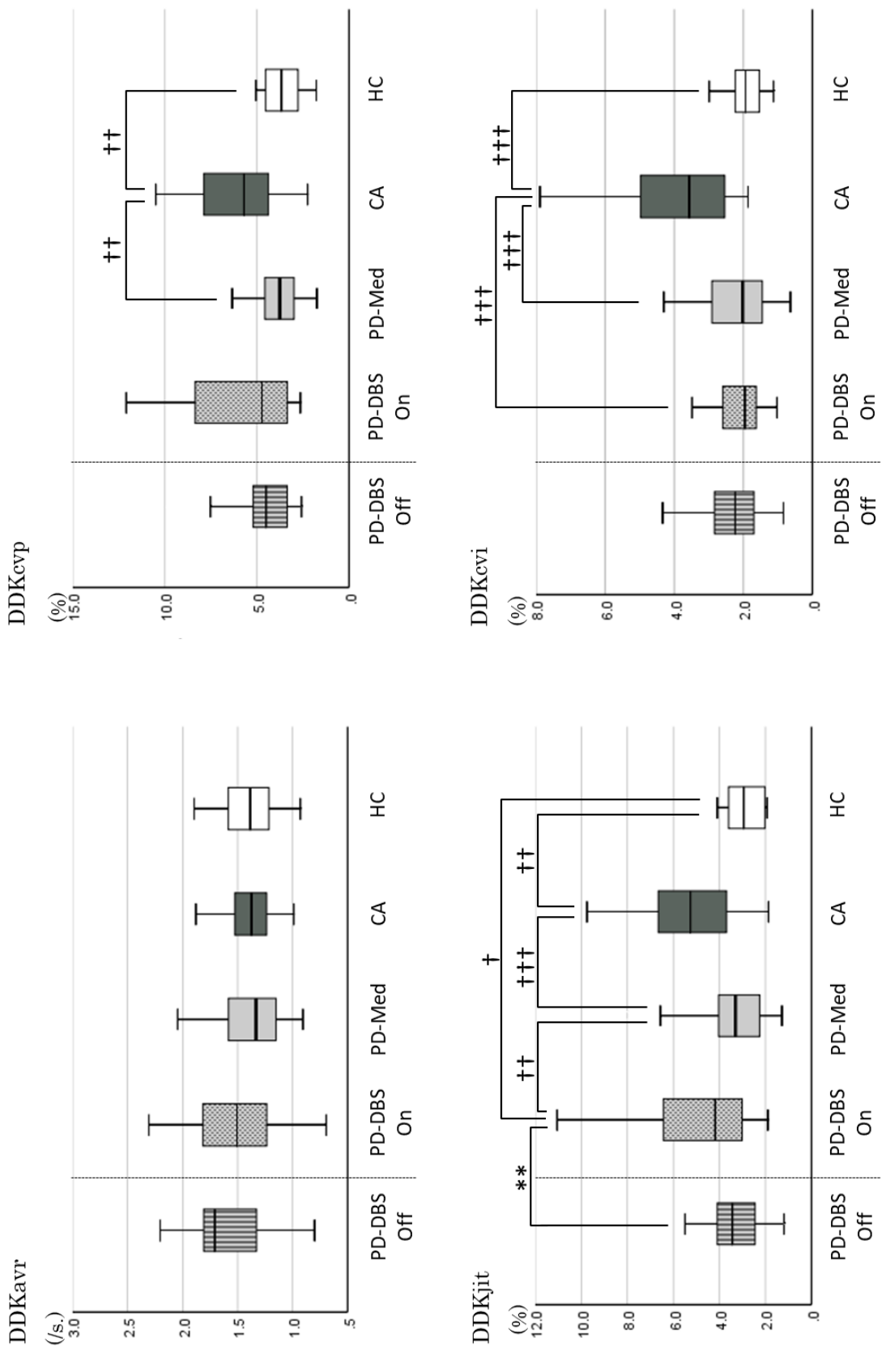
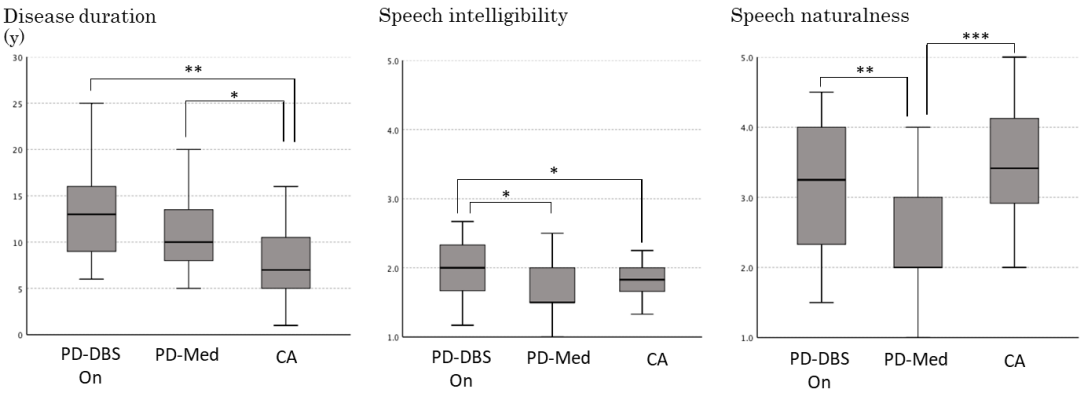
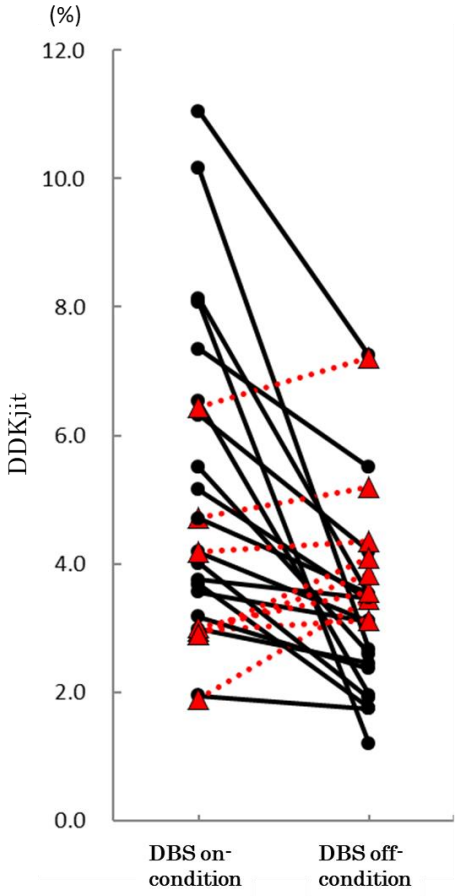


Figure 1.

Supplementary Figure



Supplementary Figure 1.



Supplementary Figure 2.