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RESEARCH PAPER

Distinct phenotypes of speech and voice disorders in Parkinson's disease after subthalamic nucleus deep brain stimulation

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ABSTRACT

Objectives To elucidate the phenotypes and pathophysiology of speech and voice disorders in Parkinson's disease (PD) with subthalamic nucleus deep brain stimulation (STN-DBS).

Methods We conducted a cross-sectional study on 76 PD patients treated with bilateral STN-DBS (PD-DBS) and 33 medically treated PD patients (PD-Med). Speech and voice functions, electrode positions, motor function and cognitive function were comprehensively assessed. Moreover, speech and voice functions were compared between the on-stimulation and off-stimulation conditions in 42 PD-DBS patients.

Results Speech and voice disorders in PD-DBS patients were significantly worse than those in PD-Med patients. Factor analysis and subsequent cluster analysis classified PD-DBS patients into five clusters: relatively good speech and voice function type, 25%; stuttering type, 24%; breathy voice type, 16%; strained voice type, 18%; and spastic dysarthria type, 17%. STN-DBS ameliorated voice tremor or low volume; however, it deteriorated the overall speech intelligibility in most patients. Breathy voice did not show significant changes and stuttering exhibited slight improvement after stopping stimulation. In contrast, patients with strained voice type or spastic dysarthria type showed a greater improvement after stopping stimulation. Spastic dysarthria type patients showed speech disorders similar to spastic dysarthria, which is associated with bilateral upper motor neuron involvement. Strained voice type and spastic dysarthria type appeared to be related to current diffusion to the corticobulbar fibres.

Conclusions Stuttering and breathy voice can be aggravated by STN-DBS, but are mainly due to aging or PD itself. Strained voice and spastic dysarthria are considered corticobulbar side effects.

INTRODUCTION

Despite improved motor function after subthalamic nucleus deep brain stimulation (STN-DBS), Parkinson's disease (PD) patients sometimes develop speech and voice disorders, which reduce patient's quality of life. A systematic review of the literature reported that stimulation-related dysarthria was observed in 9.3% of PD patients with STN-DBS.[1] A prospective study focusing on speech function revealed that PD patients with STN-DBS showed a greater deterioration in speech intelligibility at 1 year after surgery than medically treated patients.[2] Current diffusion to the cerebellothalamic fibres[2–5] and corticobulbar fibres[6–9] is closely related to speech and voice disorders. Tripoliti *et al*[10] noted that after STN-DBS, voice could sometimes sound strained, strangled and breathless, resulting in a scanning, 'one-word-at-a-time' speech. Tommasi *et al*[9] characterised dysarthria due to the corticobulbar side effect by hypophonic, slurred speech, rapid fatiguing and hesitation with frequent, long pauses. Stuttering worsened or relapsed after STN-DBS.[11 12]

Thus, STN-DBS can induce or aggravate widely different types of speech and voice disorders. However, there have been no reports that investigated the diverseness of speech and voice disorders in a large number of PD patients with STN-DBS. In this study, we assessed speech and voice functions in 76 PD patients with STN-DBS as well as 33 medically treated patients, and we aimed to divide patients with STN-DBS into several phenotypes by factor analysis and subsequent cluster analysis. Motor and cognitive functions and electrode positions were also evaluated to elucidate the underlying pathophysiology of speech and voice disorders.

METHODS

Subjects

Patients with PD who had undergone bilateral STN-DBS were recruited in the Movement Disorders Clinic of the Nagoya University Hospital from 2005 to 2013. The inclusion criteria were as follows: (1) diagnosis of PD according to the UK Parkinson's Disease Society brain bank criteria,[13] (2) ≥6-month follow-up period after subthalamic implantation, (3) absence of further neurological disease, and (4) absence of severe cognitive impairment or psychiatric disorders that may hinder speech and voice assessment. A total of 76 eligible PD patients treated with STN-DBS participated in this study (PD-DBS group). Surgical procedures were performed as previously described.[14] PD-DBS patients were evaluated in the on-state under their usual optimised medication and STN-DBS. Age, sex, disease duration and motor and cognitive function matched those of 33 patients with medically

Table 1 Clinical background of PD-DBS and PD-Med groups

	PD-DBS n=76	PD-Med n=33
Age (years)	66.1±8.4	67.9±7.4
Sex (female, %)	60.5	60.6
Disease duration (years)	14.8±5.3	14.2±4.7
Postsurgery period (years)	2.5±2.1	
UPDRS-III	23.3±11.2	23.9±10.8
UPDRS-IV	4.7±3.9	4.8±2.8
MMSE	26.3±3.4	26.0±3.3
MoCA	21.1±4.7	22.5±5.0
Line orientation	14.5±3.5	15.6±3.4
Stroop color-word test	31.5±42.2	30.6±38
Verbal fluency (semantic)	10.2±3.7*	14.8±5.9
Verbal fluency (phonemic)	7.0±3.0*	8.7±3.4
Digit span test	10.5±2.9	10.8±2.4
LEDD (mg)	660.9±365.2*	949.3±451.7
Amplitude: left (V)	2.4±0.5	
Frequency: left (Hz)	136.3±18.2	
Pulse width: left (microseconds)	89.7±16.3	
Amplitude: right (V)	2.4±0.5	
Frequency: right (Hz)	134.7±23.9	
Pulse width: right (microseconds)	91.5±18.6	
Monopolar/Bipolar/Both monopolar and bipolar (n)	47/17/12	

Values are mean±SD. Groups were compared using independent t tests or non-parametric Mann-Whitney U tests. p Value<0.05 was considered significant.
*Significant difference between two groups.
LEDD, levodopa equivalent daily dose; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PD-DBS, patients treated with deep brain stimulation; PD-Med, medically treated patients; UPDRS, Unified Parkinson's Disease Rating Scale.

treated PD were also included (PD-Med group). PD-Med patients were assessed in the on-state under continued medication. The sample characteristics are described in table 1. This study was approved by the ethics committee of the Nagoya University Graduate School of Medicine. All participants provided written informed consent.

Speech and voice evaluation

Sustained-vowels, reading task of a standard passage (The North Wind and the Sun) in Japanese, and short conversations were recorded using Computerised Speech Lab (Kay Elemetrics, Lincoln Park, New Jersey, USA) and a microphone (ECM-MS907; Sony, Tokyo, Japan) with a sampling rate of 44.1 kHz in a sound-treated room. Speech disorders were perceptually evaluated using the Assessment of Motor Speech for Dysarthria (AMSD) which comprises analogous variables developed by Darley *et al*.[15 16] Voice disorders were perceptually evaluated using the Grade of dysphonia, Roughness, Breathiness, Asthenia and Strain (GRBAS) scale.[17] Three well-trained and certified speech pathologists independently and blindly rated recorded speech samples. The scores of the three raters were averaged subsequently. Inter-rater reliability was assessed using Cohen's κ coefficient (R, http://www.r-project.org/), which was 0.745. According to the Landis and Koch classification, this fit was considered to be substantial. With regard to on-stimulation and off-stimulation assessment, changes in variables by ≥1.00 were considered as significant. The Stuttering Severity Instrument-3 (SSI-3) was used to assess the severity of stuttering.[18] Maximum phonation time (MPT) was determined by measuring the duration of the sustained vowel/a:/ after maximum inspiration.[19] A subjective self-assessment of speech and voice disorders was scored according to the Voice Handicap Index (VHI).[20] Definitions and interpretations of the variables used to evaluate speech and voice disorders are summarised in online supplementary table S1.

Speech and voice assessment in the on-stimulation and off-stimulation conditions

In 42 of 76 PD-DBS patients who agreed to stop stimulation temporarily, speech and voice functions were evaluated in the on-stimulation condition and 30 min after stopping stimulation.

Clinical and radiological evaluations

Motor function (the Unified Parkinson's Disease Rating Scale III (UPDRS-III) and UPDRS-IV) and cognitive function (the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), line orientation, Stroop color-word test, verbal fluency and digit span tests) were assessed. Levodopa equivalent daily dose (LEDD) was calculated as described previously.[21]

Postoperative CTs (Asteion; Toshiba Medical Systems, Tochigi, Japan) with a slice thickness of 1 mm were obtained concurrently with clinical evaluations. Anatomical locations of DBS electrodes were identified by fusing the postoperative CT images with the preoperative MRI (iPlan Stereotaxy; Brainlab, Munich, Germany). The lateral distance from the midline and the anteroposterior distance from the mid-commissural line to each electrode at the level of 3.5 mm below the AC–PC line were calculated and plotted on the human brain atlas.[22]

Statistical analysis

The normal distribution of data was tested using the Shapiro-Wilk test. The clinical background and speech and voice functions of PD-DBS and PD-Med patients were compared using independent t tests or non-parametric Mann-Whitney U tests. Exploratory factor analysis (generalised least-squares method) was performed on the speech and voice variables of PD-DBS patients to extract factors, followed by Varimax rotation. Fits of the data for the final factor solution were examined using the Kaiser-Meyer-Olkin measure of sampling adequacy and Bartlett's test of sphericity. Components with eigenvalues >1 were selected. Subsequently, cluster analysis (Ward's method) on the basis of the factor scores classified PD-DBS patients into clusters according to the similarity of predominant speech and voice characteristics in each patient. Two-way ANOVA with post hoc tests (Tukey or Games-Howell) or non-parametric Kruskal-Wallis tests with post-hoc tests (Mann-Whitney) were used to examine the differences among the clusters and PD-Med patients. Speech and voice functions in the on-stimulation and off-stimulation conditions were compared using paired t tests or non-parametric Wilcoxon signed rank tests. p Values <0.05 were considered significant. Abovementioned statistical analyses were performed using the Predictive Analysis Software, V.18 (SPSS, Chicago, Illinois, USA).

RESULTS

Global population characteristics

The clinical background was not significantly different between PD-DBS and PD-Med patients, except that semantic and phonemic verbal fluency were significantly worse in PD-DBS patients than those in PD-Med patients and that LEDD was significantly lower in PD-DBS patients than that in PD-Med patients (table 1). Several speech and voice variables were significantly

Table 2 Severity of speech and voice disorders in PD-DBS and PD-Med groups

	PD-DBS n=76	PD-Med n=33
AMSD		
Overall severity of speech disorders		
Intelligibility	2.7±1.0*	1.7±0.8
Naturalness	3.6±1.0*	2.4±1.0
Subparts		
Imprecise consonants	1.0±0.9*	0.4±0.4
Monoloudness	1.3±0.9	1.1±0.8
Monopitch	1.4±0.9	1.1±0.8
Low volume	1.5±0.9*	0.9±0.8
Short rushes of speech	1.0±1.0*	0.4±0.7
Voice tremor	0.4±0.5*	0.7±0.7
Sound repeated	0.7±0.8	0.6±0.6
Hypernasality	0.8±0.8*	0.3±0.5
Abnormal rate	1.1±0.8*	0.6±0.7
Variable rate	1.1±0.7	0.8±0.6
Excess loudness variation	1.1±0.7*	0.8±0.5
Abnormal pitch level	1.0±0.7*	0.5±0.5
Variable pitch	0.5±0.7*	0.1±0.2
GRBAS scale		
Overall severity of voice disorders		
Grade of dysphonia	2.0±0.7*	1.3±0.6
Subparts		
Roughness	1.3±0.7*	0.9±0.5
Breathiness	1.1±0.8	0.9±0.8
Asthenia	1.1±0.8*	0.7±0.8
Strain	1.0±0.8*	0.3±0.4
SSI-3	6.3±7.2	5.4±7.2
MPT (s)	18.7±9.2	19.6±8.8
VHI	52.5±27.9*	30.6±21.2

Values are means±SD. Groups were compared using independent t tests or non-parametric Mann-Whitney U tests. p Value<0.05 was considered significant.
*Significant difference between two groups.
AMSD, Assessment of Motor Speech for Dysarthria; GRBAS, Grade of dysphonia, Roughness, Breathiness, Asthenia and Strain; MPT, maximum phonation time; PD-DBS, patients treated with deep brain stimulation; PD-Med, medically treated patients; SSI-3, Stuttering Severity Instrument-3; VHI, Voice Handicap Index.

worse in PD-DBS patients than in PD-Med patients; and voice tremor was significantly better in PD-DBS patients than in PD-Med patients (table 2).

Factor analysis followed by cluster analysis

Exploratory factor analysis was performed on all objective speech and voice variables (AMSD, GRBAS scale, SSI-3, and MPT) from PD-DBS patients. Intelligibility, naturalness and grade of dysphonia were dropped because of cross-loadings on several factors; abnormal rate and abnormal pitch level were dropped because they partially overlapped with variable rate and variable pitch, respectively; and voice tremor was dropped because its contribution to the overall instrument was of little importance. The final factor analysis extracted five factors with eigenvalues >1.092, which together, accounted for 74.4% of the total variation. The factor-loading matrix after Varimax rotation is shown in table 3. The Kaiser-Meyer-Olkin measure of the final factor solution was 0.654, and the result of Bartlett's test of sphericity was significant ($p<0.001$), indicating the appropriateness of this factor analysis. Cluster analysis on the basis of the factor scores classified the 76 patients into five clusters.

Table 3 Factor loading matrix of the five factors after orthogonal rotation

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Sound repeated	**0.983**	−0.146	−0.109	0.008	0.013
SSI-3	**0.915**	−0.128	0.073	−0.026	0.077
Variable rate	**0.390**	−0.073	0.165	0.208	−0.141
Asthenia	−0.145	**0.917**	−0.008	0.086	0.184
Low volume	−0.252	**0.722**	0.294	0.160	0.206
Breathiness	−0.065	**0.679**	0.096	0.045	0.176
Short rushes of speech	−0.036	0.334	**0.892**	0.128	0.141
Strain	0.040	−0.018	**0.654**	0.294	0.124
Roughness	0.129	−0.152	**0.435**	0.130	0.305
MPT	0.131	−0.258	**−0.399**	−0.228	−0.199
Imprecise consonants	0.018	0.166	0.232	**0.945**	0.157
Hypernasality	0.016	0.089	0.166	**0.656**	0.158
Monopitch	0.014	0.323	0.265	0.188	**0.888**
Monoloudness	0.039	0.457	0.187	0.214	**0.755**
Excess loudness variation	−0.065	−0.044	0.286	0.113	**−0.360**
Variable pitch	−0.006	−0.043	0.133	0.083	**−0.222**

The generalised least-squares method was applied to extract factors, followed by orthogonal (Varimax) rotation.
The highest factor loadings in each variable are written in bold characters.
MPT, maximum phonation time; SSI-3, Stuttering Severity Instrument-3.

Characterisation of the clusters

The clinical background of the five clusters and PD-Med patients is summarised in online supplementary table S2. Cluster 5 had significantly longer postsurgery period and worse scores for UPDRS-III and MMSE than cluster 1. Clusters 2, 3, 4 and 5 showed significantly worse scores for semantic verbal fluency than PD-Med patients. LEDD in cluster 2 was significantly lower than that in PD-Med patients. Stimulation parameters were not significantly different among clusters.

The characteristics of speech and voice disorders in the clusters and PD-Med patients are listed in table 4. Cluster 1 included 25% of PD-DBS patients, who showed generally better speech and voice functions than patients in the other clusters. Furthermore, voice tremor scores in cluster 1 were significantly better than those in PD-Med patients. We labelled cluster 1 as 'relatively good speech and voice function type.'

Cluster 2 included 24% patients and was characterised by the highest scores for sound repeated, abnormal rate and SSI-3. We labelled cluster 2 as 'stuttering type.'

Cluster 3 included 16% patients, and scores for low volume, grade of dysphonia, breathiness and asthenia were the highest among all clusters. We labelled cluster 3 as 'breathy voice type.'

Cluster 4 included 18% patients and was characterised by the highest scores for short rushes of speech, excess loudness variation, roughness and strain and the lowest scores for MPT. We labelled cluster 4 as 'strained voice type.'

Cluster 5 included 17% patients who had the highest scores for intelligibility and naturalness, imprecise consonants, monoloudness, monopitch, hypernasality and VHI. We labelled cluster 5 as 'spastic dysarthria type.' The naming of the clusters will be discussed below.

On-stimulation and off-stimulation assessment

Forty-two PD-DBS patients consented to stopping stimulation temporarily. Since two patients became almost speechless due to severe akinesia and rigidity, speech and voice functions in 40 patients were compared between the on-stimulation and

Table 4 Severity of speech and voice disorders in the five clusters and PD-Med patients

	Cluster 1 Relatively good speech and voice function type n=19 (25%)	Cluster 2 Stuttering type n=18 (24%)	Cluster 3 Breathy voice type n=12 (16%)	Cluster 4 Strained voice type n=14 (18%)	Cluster 5 Spastic dysarthria type n=13 (17%)	PD-Med n=33
AMSD						
Overall severity of speech disorders						
Intelligibility	1.7±0.3*	2.4±0.6†	2.7±0.7‡†	3.3±0.9‡†	3.7±0.8‡†	1.7±0.8
Naturalness	2.3±0.5*	3.5±0.8‡†	4.0±0.5‡†	4.3±0.6‡†	4.4±0.6‡†	2.4±1.0
Subparts						
Imprecise consonants	0.4±0.5*	0.9±0.8*	0.6±0.4*	1.1±0.9†	2.2±0.6‡†	0.4±0.4
Monoloudness	0.4±0.5*	1.2±0.7*	1.9±0.5‡	1.5±0.8‡	2.2±0.3‡†	1.1±0.8
Monopitch	0.5±0.4*	1.2±0.9	1.8±0.6‡†	1.6±0.8‡	2.2±0.3‡†	1.1±0.8
Low volume	0.9±0.5*	1.0±0.7*	2.3±0.4‡†	1.8±1.0	2.0±0.7‡†	0.9±0.8
Short rushes of speech	0.2±0.3*	0.5±0.5*	1.0±0.5‡	2.5±0.6‡†	1.5±0.8‡†	0.4±0.7
Voice tremor	0.2±0.4**	0.4±0.5	0.3±0.4	0.8±0.7‡	0.5±0.5	0.7±0.7
Sound repeated	0.3±0.4*	1.7±0.7‡†	0.1±0.3*	0.5±0.5*	0.4±0.5*	0.6±0.6
Hypernasality	0.4±0.5*	0.7±0.7	0.3±0.5*	0.8±0.7	1.7±1.0‡†	0.3±0.5
Abnormal rate	0.6±0.5*	1.5±0.8‡†	0.8±0.7	1.2±0.8	1.4±1.0	0.6±0.7
Variable rate	0.8±0.5	1.5±0.8	0.8±0.6	1.2±0.8	1.1±0.8	0.8±0.6
Excess loudness variation	1.1±0.5	1.1±0.8	1.0±0.6	1.6±0.7†	0.9±0.5	0.8±0.5
Abnormal pitch level	0.9±0.6	0.8±0.6	1.3±0.7†	1.1±0.8	1.2±0.8	0.5±0.5
Variable pitch	0.4±0.4	0.6±1.0	0.3±0.6	0.6±0.7	0.4±0.5	0.1±0.2
GRBAS scale						
Overall severity of voice disorders						
Grade of dysphonia	1.2±0.4*	1.8±0.6†	2.5±0.4‡†	2.4±0.5‡†	2.3±0.5‡†	1.3±0.6
Subparts						
Roughness	0.9±0.6*	1.3±0.7	1.1±0.6	1.7±0.7‡†	1.5±0.7†	0.9±0.5
Breathiness	0.6±0.5*	1.0±0.7*	2.0±0.5‡	1.1±0.8	1.3±0.8	0.9±0.8
Asthenia	0.6±0.4*	0.9±0.8*	2.2±0.5‡†	1.0±0.7*	1.5±0.7‡†	0.7±0.8
Strain	0.5±0.4*	0.7±0.6*	0.6±0.6*	1.9±0.8‡†	1.5±0.8†	0.3±0.4
SSI-3	2.6±3.3*	13.4±7.8‡†	2.3±5.4*	6.8±6.4	3.8±4.7*	5.0±6.9
MPT (s)	23.1±7.1*	22.0±9.3*	19.1±8.1	13.4±9.0‡	14.3±5.9‡	19.6±8.8
VHI	32.8±21.1*	49.9±28.6	53.3±21.8	65.8±27.4‡†	74.2±21.7‡†	30.6±21.2

Values are mean±SD. Groups were compared using two-way ANOVA with post hoc tests (Tukey or Games-Howell), or non-parametric Kruskal-Wallis tests with post hoc tests (Mann-Whitney). p Value <0.05 was considered significant.
*Significantly better than other cluster groups.
†Significant difference between the clusters and PD-Med.
‡Significantly worse than other cluster groups.
AMSD, Assessment of Motor Speech for Dysarthria; GRBAS, Grade of dysphonia, Roughness, Breathiness, Asthenia, and Strain; MPT, maximum phonation time; PD-Med, medically treated patients; SSI-3, Stuttering Severity Instrument-3; VHI, Voice Handicap Index.

off-stimulation conditions. The spider diagrams of the clusters and PD-Med patients are shown in figure 1, and the results of statistical analyses are included in online supplementary table S3. Speech and voice functions tended to improve in the off-stimulation condition, and statistically significant changes in several variables were observed between the on-stimulation and off-stimulation conditions. With regard to the representative speech or voice variable of each group, in cluster 2, the score for sound repeated improved significantly after stopping stimulation (p=0.010); in cluster 3, the score for breathiness tended to improve, albeit not significantly (p=0.144); in cluster 4, the score for strain improved significantly (p=0.018); and in cluster 5, the score for imprecise consonants improved significantly (p=0.027).

With regard to individual analyses, speech intelligibility significantly improved in eight patients (20%) after stopping stimulation, and significantly deteriorated in one patient (2.5%; figure 2A). With regard to low volume, significant improvement was observed in 11 patients (27.5%), and significant deterioration was observed in five patients (12.5%; figure 2B). In cluster 2, two of nine patients (22.2%) showed significant improvement in sound repeated after stopping stimulation (figure 2C). In cluster 3, one of four patients (25%) showed significant improvement in breathiness (figure 2D). In cluster 4, four of eight (50%) patients showed significant improvement in strain (figure 2E). Finally, in cluster 5, four of eight (50%) patients experienced significant improvement in imprecise consonants (figure 2F).

Association between the clusters and electrode positions

The electrode positions were available for 68 of 76 PD-DBS patients. Clusters 1, 4, and 5 tended to have a higher proportion of electrodes positioned laterally to STN than clusters 2 and 3 (figure 3).

DISCUSSION

In the present study, we comprehensively investigated the characteristics of speech and voice disorders in 76 PD-DBS patients and 33 PD-Med patients. The clinical background of PD-DBS and PD-Med patients were not significantly different with the exception of worse semantic and phonemic verbal fluency and lower LEDD in PD-DBS patients. This may be explained by the negative effects of STN-DBS on verbal fluency[23] and the effects of LEDD reduction of STN-DBS.

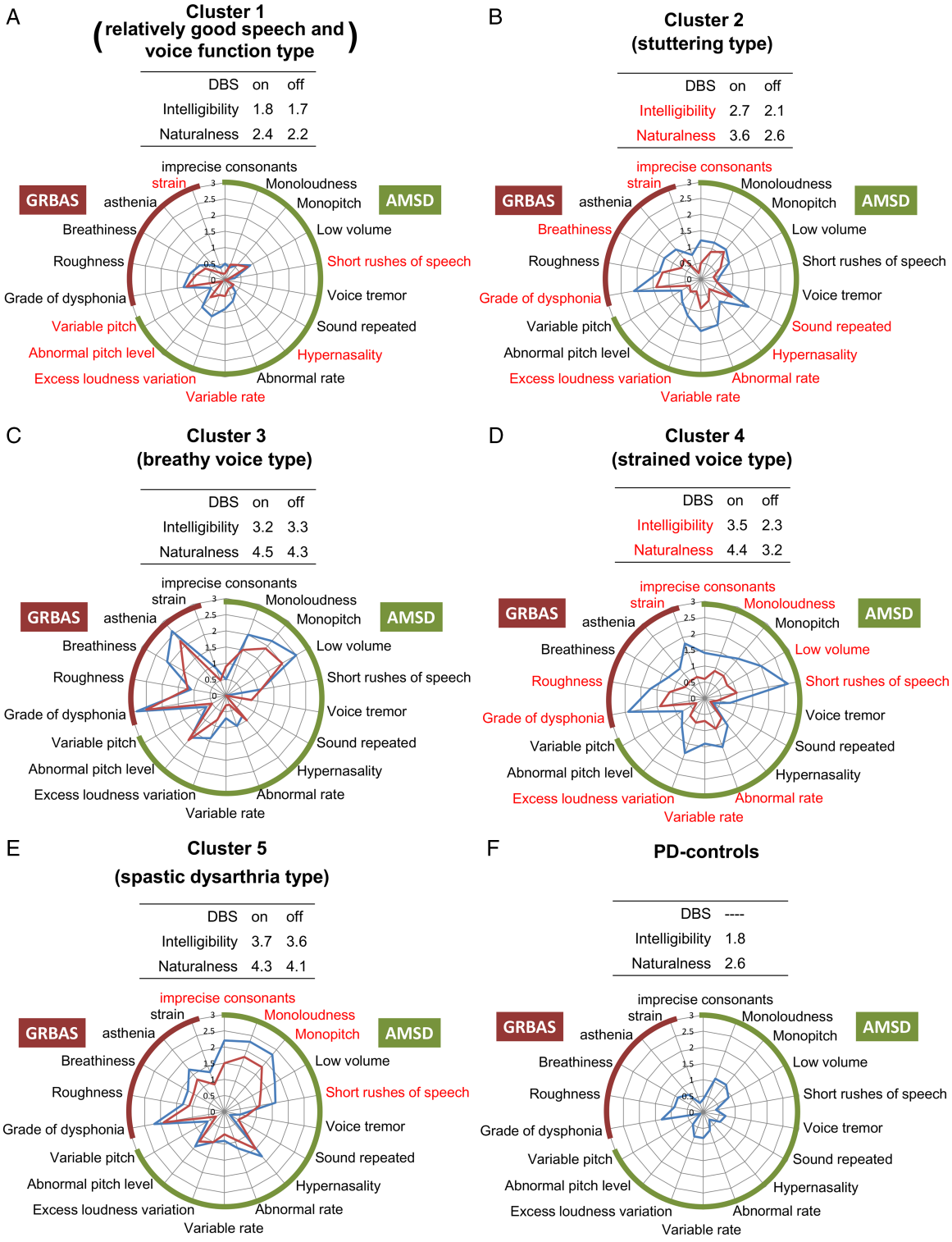

Figure 1 Spider diagrams of speech and voice variables in the five clusters and PD-Controls. Higher scores indicate worse condition. Cluster 1 (A); cluster 2 (B); cluster 3 (C); cluster 4 (D); cluster 5 (E); and PD-Med (F) are shown. With regard to the five clusters, spider diagrams of speech and voice disorders in the on and off stimulation conditions are indicated in blue and red, respectively. The overall grades of severity (intelligibility and naturalness) are shown above each spider diagram. The variables that changed significantly after stopping stimulation are marked in red.

PD-DBS patients had significantly more severe speech and voice disorders than PD-Med patients. Voice tremor was the only variable that was significantly better in PD-DBS patients compared with that in PD-Med patients. Furthermore, speech intelligibility improved significantly in 20% and deteriorated significantly in 2.5% of patients after stopping stimulation. Low volume improved significantly in 27.5% and deteriorated significantly in 12.5% of patients. Reportedly, STN-DBS improves loudness or voice tremor presumably due to the ameliorating effect on hypokinesia, rigidity, and tremor in speech-related organs[6 24–27]; however, overall speech intelligibility remains unchanged[24 26] or even worsens because of STN-DBS.[2 6] Our findings are in agreement with these reports.

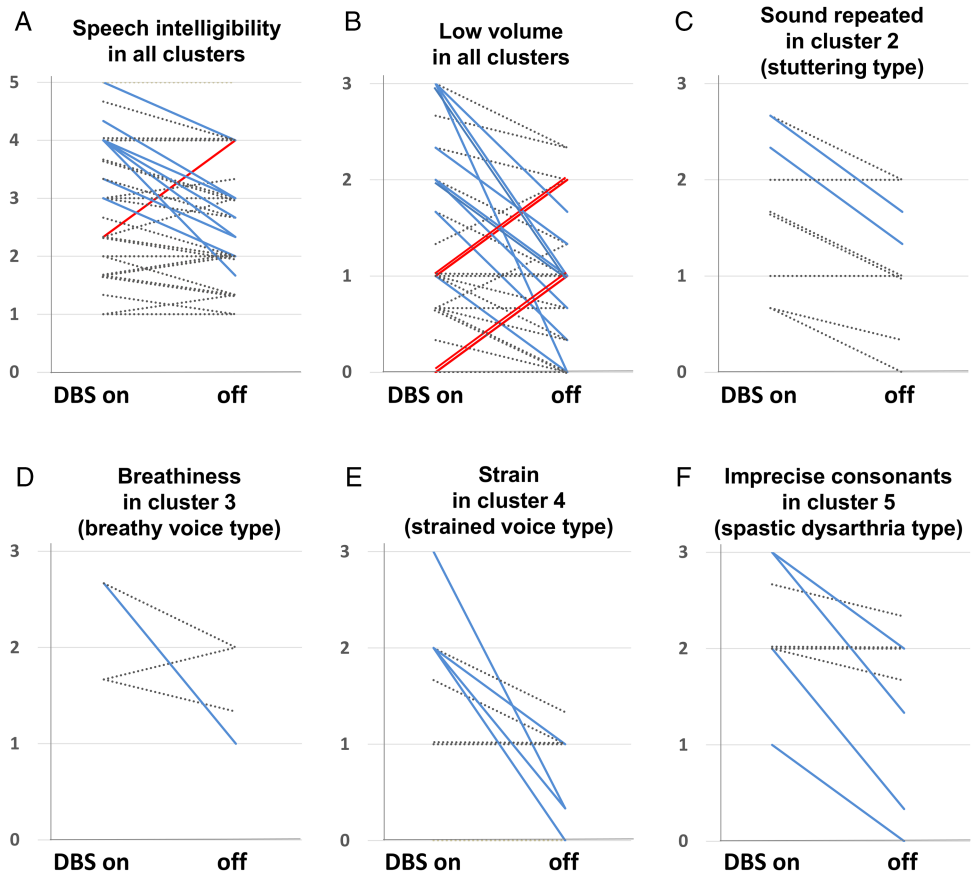

Figure 2 Changes in speech intelligibility (A) and low volume (B) between the on and off stimulation conditions are shown for the 40 patients who underwent on and off stimulation evaluation. Sound repeated in cluster 2 (C); breathiness in cluster 3 (D); strain in cluster 4 (E); and imprecise consonants in cluster 5 (F) were also compared between the on and off stimulation conditions. The blue lines indicate significant improvement (≥1.00), red lines indicate significant worsening (≥1.00) and grey dotted lines represent no significant changes.

Medically treated PD patients frequently have hypokinetic dysarthria, which predominantly consists of monoloudness, monopitch, reduced stress, short rushes of speech, imprecise consonants and breathy and harsh voice.[16] These variables were elevated to varying degrees in each cluster, in the on-stimulation and off-stimulation conditions, suggesting that PD-DBS patients have hypokinetic dysarthria.

Factor analysis and subsequent cluster analysis classified PD-DBS patients into five clusters according to the phenotypes of their speech and voice disorders. These distinct phenotypes most likely resulted from the diversity in the mechanisms that underlie PD and in the influence of STN-DBS.

Cluster 1: relatively good speech and voice function type

Cluster 1 showed better speech and voice functions than the other clusters. Speech and voice functions in cluster 1 were roughly equal to those in PD-Med patients, with the exception of significantly better scores for voice tremor in cluster 1. Speech and voice functions tended to improve after stopping stimulation; however, their changes were relatively small in comparison with the other clusters. Therefore, we labelled cluster 1 as 'relatively good speech and voice function type.'

Cluster 2: stuttering type

Cluster 2 patients were characteristically associated with 'stuttering.' The score for sound repeated improved significantly after stopping stimulation; however, in individual analysis, only 22.2% of patients showed significant improvement after stopping stimulation. Stuttering is considered to be related to dysfunction of the basal ganglia-thalamocortical motor network[28] and is frequently observed in advanced PD patients.[29] Furthermore, some case reports have described improvement in stuttering[30] and worsening of stuttering[11 12] after STN-DBS. In conclusion, stuttering in cluster 2 patients was assumed to be primarily because of degeneration of the basal ganglia-thalamocortical motor network; STN-DBS can potentially affect stuttering.

Cluster 3: breathy voice type

Cluster 3 patients had the highest scores for grade of dysphonia, breathiness, asthenia and low volume, indicating laryngeal dysfunction. Previous laryngoscopic studies have demonstrated incomplete glottal closure in 60%–67% of PD patients,[31 32] which is probably because of impaired control of laryngeal muscles or age-related vocal fold changes. Air leakage through the glottis is perceived as breathiness[17] and contributes to asthenia and low volume. Therefore, we labelled cluster 3 as 'breathy voice type.' Cluster 3 patients showed a tendency for improvement (albeit not significant) in several variables after stopping stimulation. In individual analysis, breathiness was significantly improved in only one patient. In conclusion, cluster 3 patients appeared to have breathy voice mainly due to aging or PD itself; STN-DBS can potentially aggravate breathy voice.

Cluster 4: strained voice type

Voice in cluster 4 sounded strained, strangled and very effortful, which appeared to have contributed to high scores for short rushes of speech, excess loudness variation and short MPT.

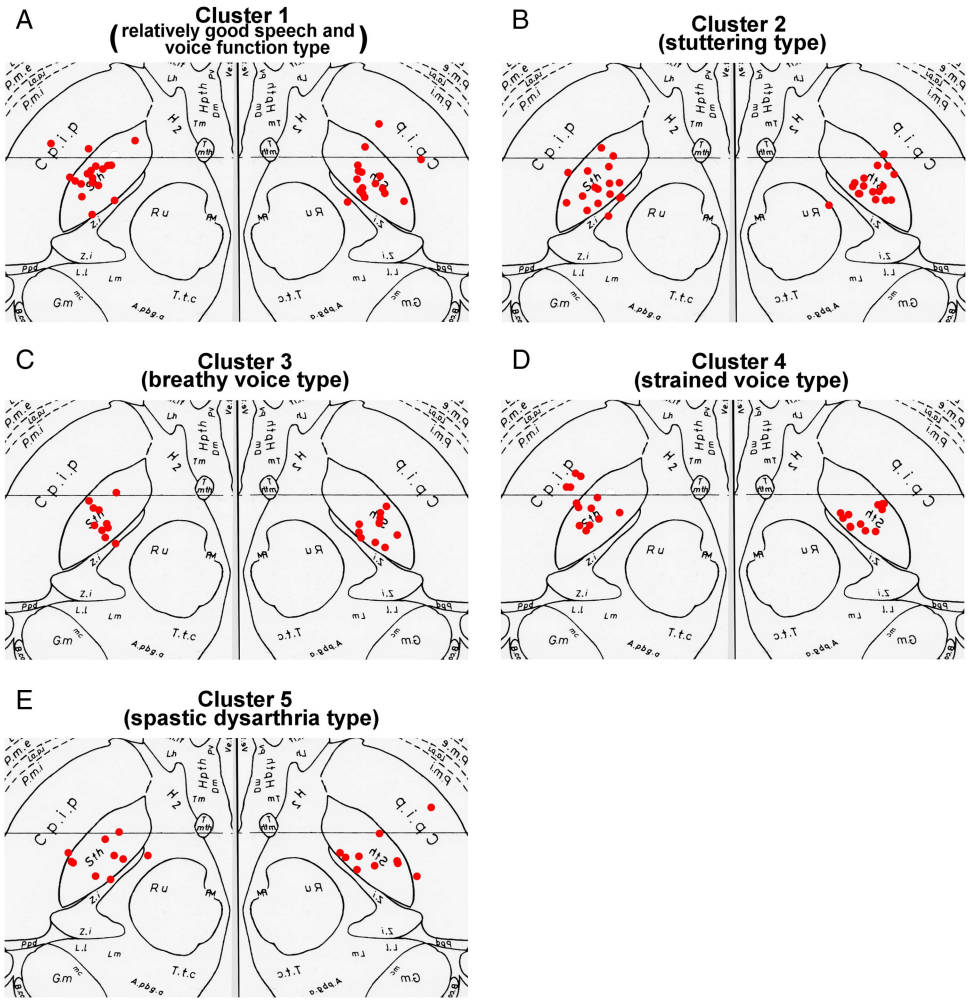

Figure 3 Electrode positions in the five clusters are plotted on the axial view at the level of 3.5 mm below the AC–PC line. Electrode positions are shown for 18 patients in cluster 1 (A); 17 patients in cluster 2 (B); 10 patients in cluster 3 (C); 10 patients in cluster 4 (D); and 13 patients in cluster 5.

Therefore, we labelled cluster 4 as 'strained voice type.' Cluster 4 exhibited the largest improvement after stopping stimulation among the clusters. In individual analysis, 50% of patients showed significant improvement in strain after stopping stimulation, and strain tended to improve in the remaining patients. Strained voice quality is uncommon in medically treated PD patients and is reportedly associated with hypertonicity of the laryngeal muscles.[33] Stimulation of the corticobulbar and corticospinal tracts induces a tonic muscle contraction that mimics fixed dystonia in the face and limbs and causes speech disorders.[9] Current diffusion to the corticobulbar fibres may cause abnormal tonic laryngeal muscle contraction, which resulted in strained voice quality.

Cluster 5: spastic dysarthria type

Cluster 5 patients showed the highest scores for imprecise consonants and hypernasality, which are common in spastic dysarthria. Therefore, we labelled cluster 5 as 'spastic dysarthria type.' Spastic dysarthria is associated with bilateral upper motor neuron involvement.[16] A relationship between current diffusion to the corticobulbar fibres and speech and voice disorders has been mentioned.[6–9] Furthermore, in individual analysis, 50% of patients showed significant improvement in imprecise consonants after stopping stimulation. These results indicate that spastic dysarthria type is likely related to current diffusion to the corticobulbar fibres.

Association between speech and voice disorders and electrode positions

Given that clusters 4 and 5 tended to have a higher proportion of electrodes located laterally to STN than those in clusters 2 and 3, strained voice type and spastic dysarthria type were most likely related to current diffusion to the corticobulbar fibres. The corticobulbar fibres were believed to pass through the genu of the internal capsule. However, a recent study using diffusion tensor imaging has demonstrated that corticobulbar fibres pass through the posterior limb of the internal capsule, which is closer to the STN than the genu of the internal capsule.[34] With regard to strained voice type, STN-DBS may mainly affect the laryngeal muscles. In contrast, with regard to spastic dysarthria type, STN-DBS may mainly affect the lip, tongue and velum. This can be explained by individual differences in the corticobulbar tracts and electrical field generated by DBS. Interestingly, cluster 1 had relatively good speech and voice functions, and also tended to have a high proportion of laterally-located electrodes and had stimulation parameters similar to those of clusters 4 and 5. This finding suggests aetiologies other than electrode positions. Tripoliti *et al*[2 3] demonstrated that longer disease duration and a higher preoperative on-medication

UPDRS-III score were predictive factors for postoperative deterioration of speech intelligibility. Additionally, speech and voice functions progressively deteriorate over time after implantation[35] probably due to both progression of brain degeneration and the stimulation effect. Longer disease duration, longer post-surgery period, and worse motor and cognitive functions may contribute to worse speech and voice functions in clusters 4 and 5 in comparison with cluster 1. Further prospective studies will be needed to elucidate this issue. Although we did not find an association between medially located electrodes and speech and voice disorders, some researchers have reported that medially located electrodes may lead to speech deterioration as a result of current diffusion to the cerebellothalamic fibres.[2–5] This can be another pathophysiological mechanism of stimulation-related speech and voice disorders.

The relationship between electrode positions and speech and voice disorders in clusters 2 and 3 was not found. Additionally, most patients in clusters 2 and 3 did not experience significant improvement after stopping stimulation. These findings indicate that speech and voice disorders in clusters 2 and 3 are mainly due to PD itself.

Therapies for speech and voice disorders after STN-DBS

Our findings suggest that stuttering and breathy voice can be aggravated by STN-DBS, but are mainly due to PD itself, and that strained voice and spastic dysarthria, which are uncommon in medically treated PD patients, are related to current diffusion to the corticobulbar fibres. Moreover, the patients were thought to principally have hypokinetic dysarthria in common. One patient can combine more than two phenotypes (eg, a patient with hypokinetic dysarthria, stuttering and spastic dysarthria). This is an important point in determining how to treat patients' speech and voice disorders.

The Lee Silverman Voice Treatment (LSVT) is an efficacious treatment for hypokinetic dysarthria in medically treated PD patients.[36] However, patients treated with STN-DBS respond differently to the LSVT.[10] Before initiating the LSVT, stimulation parameters should be adjusted to eliminate the worsening effects of STN-DBS on speech and voice functions. Personalised programming approach (eg, individualised current-shaping with interleaving stimulation) or a new device (eg, directional stimulation) may reduce stimulation-related side effects without undermining the effects on the cardinal symptoms.[37 38] Patients with stuttering are thought to have difficulty in maintaining a precise rhythm of speech. Rhythm therapy such as a pacing board may be effective.[39] Based on the pathophysiology of speech and voice disorders, optimally balanced therapies comprising STN-DBS, medication, and rehabilitation are required to maximise patients' quality of life.

Methodological issues

Several limitations of this study must be considered. First, because patients were not randomised prospectively to the PD-DBS and PD-Med groups, we could not determine whether both groups were completely equivalent. Second, this study aimed to elucidate the phenotypes of speech and voice disorders in PD patients with STN-DBS in the on-state under their usual treatment. No data under unilateral stimulation are available in this study. Therefore, we could not determine how much stimulation of each side was involved in speech and voice disorders. Additionally, the impact of medication on speech and voice functions was not assessed. Furthermore, healthy controls were not involved. Third, larger changes in speech and voice disorders may be obtained with a longer off-stimulation period. Further studies are required to determine the appropriate period to evaluate speech and voice functions in the off-stimulation condition. Fourth, there is controversy over the accuracy of electrode positions identified by fusing the postoperative CT with the preoperative MRI.[40] Additionally, we did not conduct statistical analyses on electrode positions. Ideally, the distance between the active contact and the corticobulbar fibres or cerebellothalamic fibres should be calculated using diffusion tensor imaging and the relationship between the distance and the stimulation parameters should be statistically analysed. Finally, changes in speech and voice disorders over time were unclear because of the cross-sectional nature of the study. Future longitudinal research is required to clarify changes in each phenotype of speech and voice disorders over time.

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