Early detection of speech and voice disorders in Parkinson's disease patients treated with subthalamic nucleus deep brain stimulation: A 1 year follow-up study

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Abstract

We previously reported that Parkinson's disease (PD) patients treated with subthalamic nucleus deep brain stimulation (STN-DBS) had distinct phenotypes of speech and voice disorders: hypokinetic dysarthria, stuttering, breathy voice, strained voice, and spastic dysarthria. However, changes over time remain unclear. In the present study, thirty-two consecutive PD patients were assessed before and up to 1 year after surgery (PD-DBS). Eleven medically treated PD patients were also assessed (PD-Med). Speech, voice, motor, and cognitive functions were evaluated. At baseline, the incidence of hypokinetic dysarthria (63% of PD-DBS vs. 82% of PD-Med), stuttering (50% vs. 45%), breathy voice (66% vs. 73%), and strained voice (3% vs. 9%) was similar between groups. At 1 year, a slight but significant deterioration in speech intelligibility ($p < 0.001$) and grade of dysphonia ($p = 0.001$) were observed only in PD-DBS group compared with baseline. During the follow-up, stuttering (9% vs. 18%) and breathy voice (13% vs. 9%) emerged in PD-DBS and PD-Med, but strained voice (28%) and spastic dysarthria (44%) emerged only in PD-DBS. After the stimulation was stopped, strained voice and spastic dysarthria improved in most patients; while stuttering and breathy voice improved in a minority of patients. These findings indicate that the most common DBS-induced speech and voice disorders are strained voice and spastic dysarthria and that STN-DBS potentially aggravates stuttering and breathy voice. An improved understanding of these types of disorders may help detect speech and voice deterioration during the early phase and lead to appropriate treatments.

Introduction

Subthalamic nucleus deep brain stimulation (STN-DBS) is a well-established surgical treatment for advanced Parkinson's disease (PD) patients with motor complications (Deuschl et al. 2006). STN-DBS has the capacity to improve loudness or voice tremor (D'Alatri et al. 2008; Klostermann et al. 2008), probably by ameliorating hypokinesia, rigidity, and tremor in speech-related muscles. However, overall speech intelligibility remains unchanged (D'Alatri et al. 2008) or even worsens (Klostermann et al. 2008; Tripoliti et al. 2011a) after STN-DBS. Tripoliti et al. demonstrated a significant deterioration in speech intelligibility one year after STN-DBS (Tripoliti et al. 2011a). However, prospective studies employing detailed perceptual assessments of speech and voice functions are highly limited.

Up to 90% of medically treated PD patients develop speech and voice disorders during their disease course (Ho et al. 1998). These disorders are termed as hypokinetic dysarthria and are characterized by monotonous and hypophonic speech (Darley et al. 1969). In addition, 53%–54% of PD patients stutter (Benke et al. 2000; Goberman et al. 2010). In contrast, various other speech and voice disorders have been reported in patients treated with STN-DBS; they sounded "strained, strangled, and breathless (Tripoliti et al. 2011b)," had "hypophonic, slurred speech, rapid fatiguing and hesitation with frequent, long pauses (Tommasi et al. 2008)," or had "worsened stuttering (Burghaus et al. 2006)."

Recently, we conducted a cross-sectional investigation on 76 PD patients treated with STN-DBS at a mean of 2.5 years after surgery and 33 medically treated PD patients (Tsuboi et al. 2015a). A statistical approach classified speech and voice disorders in patients with STN-DBS into the five distinct phenotypes: relatively good speech and voice, stuttering, breathy voice strained voice, and spastic dysarthria. Basically, patients had hypokinetic dysarthria in common. Strained voice sounded strangled and required great effort. Speech in spastic dysarthria type was characterized by imprecise consonants and hypernasality commonly associated with corticobulbar

involvement (Darley et al. 1969). Analysis of electrode positions suggested that strained voice/spastic dysarthria were associated with the spread of current to the corticobulbar fibers. Both strained voice and spastic dysarthria improved after the stimulation was stopped. In contrast, stuttering and breathy voice were thought to be mainly due to PD itself, but could be partially aggravated by STN-DBS.

Furthermore, our laryngoscopic examination revealed a higher prevalence of incomplete glottal closure, abnormal and excess laryngeal muscle contraction, and asymmetrical glottal movement in PD patients treated with STN-DBS compared with in medically treated PD patients (Tsuboi et al. 2015b). In particular, incomplete glottal closure and abnormal laryngeal muscle contraction significantly correlated with breathy voice and strained voice, respectively. We also characterized voice and articulation features of PD patients treated with STN-DBS using acoustic analysis (Tanaka et al. 2015, 2016).

Importantly, patients can combine more than two types of speech and voice disorders (eg, a patient with hypokinetic dysarthria, stuttering and spastic dysarthria). However, it is sometimes impossible to distinguish the impact on speech and voice disorders of STN-DBS from that of PD itself without longitudinal assessments. In the present study, we performed a detailed prospective investigation of PD patients treated with and without STN-DBS to compare changes in their speech and voice disorders and to determine the time of appearance of characteristic speech and voice deterioration after STN-DBS.

Materials and Methods

Participants

This research was approved by the institutional ethics committee. Written informed consent was obtained from all the patients. The inclusion criteria were as follows: (1) diagnosis of PD according to the UK Parkinson's Disease Society brain bank criteria,(Hughes et al. 1992) (2) absence

of other neurological diseases, and (3) absence of severe cognitive impairment or psychiatric disorders that may hinder the assessment. Thirty-two consecutive PD patients were assessed before bilateral STN implantation and 3 months, 6 months, and 1 year after surgery (PD-DBS group). Speech, voice, motor, and cognitive functions of PD-DBS patients were evaluated in the on-state under their usual optimized medication and STN-DBS. Speech and voice functions were also evaluated 30 min after the stimulation was stopped. Because one patient became almost speechless due to severe akinesia and rigidity, the data of speech and voice functions in the off-stimulation condition were available from 31 patients. Among the 16 advanced medically-treated PD patients with 1-year-follow-up data, speech, voice, and cognitive function matched those of 11 patients were also analyzed (PD-Med group). These patients were assessed in the on-state under continued medication.

Surgical procedures

Preoperative 1.5 or 3 T MRI (Avanto/Trio/Skyra; Siemens, Erlangen, Germany) were co-registered with a stereotactic CT (Leksell frame; Elekta Instruments, Stockholm, Sweden) for targeting and planning the implantation trajectories (iPlan Stereotaxy; Brainlab, Munich, Germany). Electrodes (model 3389; Medtronic, Minneapolis, MN, USA) were bilaterally implanted under intraoperative microelectrode recordings and macrostimulation. Finally, pulse generators were implanted (Activa; Medtronic).

Speech and voice evaluation

Sustained-vowels, a reading task of a standard passage (The North Wind and the Sun) in Japanese, and short conversations were recorded using Computerized Speech Lab (Kay Elemetrics, Lincoln Park, NJ, 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 (Darley et al. 1969; Nishio 2004). Voice disorders were perceptually evaluated using the Grade of dysphonia, Roughness, Breathiness, Asthenia and Strain (GRBAS) scale (Hirano 1981). Each variable of the AMSD and GRBAS scale is scored from 0 to 3 (0 = normal, 1 = mild, 2 = moderate, 3 = severe), except for speech intelligibility and speech naturalness, which are scored from 1 to 5. Higher scores indicate more severe abnormalities. Definitions and interpretations of the variables are summarized in Supplementary Table 1. Three well-trained and certified speech pathologists independently and blindly rated the recorded speech samples. The median value of scores from these raters was used. Inter-rater reliability was assessed using Cohen's κ coefficient (R, http://www.r-project.org/) and found to be 0.784, which was considered to be substantial in accordance with Landis and Koch classification.

We considered that the patients had a particular type of speech and voice disorders if all the hallmark variables were ≥1 (monoloudness, monopitch, and low volume for hypokinetic dysarthria type; sound repeated for stuttering type; breathiness for breathy voice type; strain for strained voice type; and imprecise consonants and hypernasality for spastic dysarthria type) (Tsuboi et al. 2015a). Regarding the on- and off-stimulation assessment, changes in variables by ≥1 were considered as significant.

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) and Montreal Cognitive Assessment (MoCA)) were assessed. Levodopa equivalent daily dose (LEDD) was calculated as described previously (Tomlinson et al. 2010). Postoperative CTs (Asteion; Toshiba Medical Systems, Tochigi, Japan) with a slice thickness of 1 mm were performed at 3 months after surgery. Anatomical locations of DBS electrodes were identified by fusing the postoperative CT

images with the preoperative MRI (iPlan Stereotaxy). The lateral distance from midline and the antero–posterior 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 a standard human brain atlas (Schaltenbrand and Wahren 1977).

Statistical analysis

Normal distribution of data was tested using the Shapiro–Wilk test. The characteristics of PD-DBS and PD-Med were compared using independent t-tests or non-parametric Mann–Whitney U-tests, as appropriate. In PD-DBS, changes over time in speech and voice functions were assessed by comparing the data at baseline with those in the on-stimulation condition at 1 year after surgery using Wilcoxon signed-rank test. To clarify the impact of STN-DBS, differences in speech and voice functions between the on- and off-stimulation conditions were assessed using Wilcoxon signed-rank test. The incidences of types of speech and voice disorders in the two groups were compared using chi-square test or Fisher's exact test, as appropriate. A p value of <0.05 was considered significant. Statistical analysis was performed using the Predictive Analysis Software, V.18 (SPSS, Chicago, Illinois, USA).

Results

Patient characteristics

As shown in Table 1, age, age at onset, sex, UPDRS-III, MMSE, and MoCA were not significantly different between PD-DBS and PD-Med groups. PD-DBS group had significantly higher UPDRS-IV ($p = 0.006$) and LEDD ($p = 0.012$) at baseline than PD-Med group. In PD-DBS group, UPDRS-IV was significantly improved ($p < 0.001$) and LEDD was significantly reduced ($p < 0.001$) at 1 year compared with those at baseline. In PD-Med group, LEDD was significantly increased at 1 year compared with that at baseline ($p = 0.012$). PD-DBS group had significantly

better UPDRS-IV ($p < 0.001$) at 1 year than PD-Med group. The summary and the individual data of DBS parameters are shown in Table 2 and Supplementary Table 2, respectively.

Speech and voice functions

Speech and voice data at baseline and at 1 year are shown in Table 3. Changes in key variables over time are shown in Fig. 1. The data at 3 and 6 months are available in Supplementary Table 3. At baseline, speech and voice functions of the two groups did not show significant differences.

Compared with baseline, PD-DBS group showed a slight but significant deterioration in the overall grades of severity (speech intelligibility, $p < 0.001$; speech naturalness, $p < 0.001$; and grade of dysphonia, $p = 0.001$) and in several subparts (imprecise consonants, $p < 0.001$; low volume, $p = 0.020$; sound repeated, $p = 0.020$; hypernasality, $p < 0.001$; abnormal rate, $p = 0.033$; variable rate, $p = 0.005$; roughness, $p = 0.001$; asthenia, $p = 0.012$; and strain, $p = 0.008$) at 1 year. In PD-DBS group, imprecise consonants ($p = 0.011$), variable rate ($p = 0.001$), excess loudness variation ($p = 0.018$) roughness ($p = 0.018$), and strain ($p = 0.001$) in the on-stimulation condition were significantly worse than those in the off-stimulation condition at 1 year. PD-DBS group in the on-stimulation condition had significantly worse scores in grade of dysphonia ($p = 0.020$) and strain ($p = 0.005$) than PD-Med group at 1 year.

In PD-Med group, sound repeated ($p = 0.046$), abnormal rate ($p = 0.046$), and abnormal pitch level ($p = 0.025$) were significant worse and monopitch ($p = 0.025$) was significantly better at 1 year than at baseline.

Types of speech and voice disorders

Changes in the types of speech and voice disorders of each patient are shown in Fig. 2 and summarized in Table 4. 88% of PD-DBS and 91% of PD-Med groups had one or more types of speech and voice disorders at baseline. The incidence of hypokinetic dysarthria (63% of PD-DBS vs.

82% of PD-Med), stuttering (50% vs. 45%), breathy voice (66% vs. 73%), and strained voice (3% vs. 9%) was not significantly different between the two groups at baseline. During the 1-year follow-up, these pre-existing types were not resolved; and several patients developed additional types.

Strained voice (28%) and spastic dysarthria (44%) were the most common additional types in PD-DBS group. In contrast, none of PD-Med group developed these types during the follow-up. The incidence of strained voice tended to be higher ($p = 0.05$) and that of spastic dysarthria was significantly higher ($p = 0.006$) in PD-DBS group than those in PD-Med group. In PD-DBS group, strained voice and spastic dysarthria appeared at 3 months ($n = 3$; $n = 2$, respectively), after increasing the voltage/pulse width ($n = 3$; $n = 8$), after changing active contacts ($n = 2$; $n = 2$), or with stable/decreased parameters ($n = 1$; $n = 2$).

A small number of patients developed stuttering (9% of PD-DBS vs. 18% of PD-Med) and breathy voice (13% vs. 9%) during the follow-up; the incidence of these disorders was not significantly different between the two groups.

Changes in overall speech intelligibility of each PD-DBS patient is shown in Fig. 3. Seventeen patients remained stable; thirteen patients experienced one-point deterioration; one patient experienced two-point deterioration; and one patient experienced one-point amelioration during the follow-up.

After the stimulation was stopped, PD-DBS group experienced a significant improvement in strained voice (78%) or spastic dysarthria (62%). In contrast, a minority of PD-DBS group experienced a significant improvement in stuttering (22%) or breathy voice (33%). There was no significant association between electrode positions and types of speech and voice disorders (Supplementary Fig. 1).

Discussion

Approximately 90% of the patients had one or more types of speech and voice disorders at

baseline; the common types were hypokinetic dysarthria, breathy voice, and stuttering. This result is in keeping with the literature (Ho et al. 1998; Benke et al. 2000; Goberman et al. 2010). PD-DBS group experienced slight but significant deterioration in speech and voice functions during the 1-year follow-up. Strained voice and spastic dysarthria were the most common DBS-induced disorders. We emphasize the importance of identifying these types of disorders because they have distinct pathophysiologies and require different treatment strategies.

Strained voice and spastic dysarthria

Strained voice and spastic dysarthria are not common in PD patients (Darley et al. 1969) and may be typical DBS-induced speech and voice disorders (Tommasi et al. 2008; Tripoliti et al. 2011a; Tsuboi et al. 2015a). In our cohort, mild strained voice was found in only one patient in both PD-DBS and PD-Med groups at baseline. Remarkably, only patients in PD-DBS group developed strained voice (28%) and spastic dysarthria (44%) during the follow-up. These disorders emerged in some patients as early as 3 months after surgery. After the stimulation was stopped, most PD-DBS patients with these disorders showed significant improvement. Thus, the emergence of strained voice and spastic dysarthria after STN-DBS is thought to be strongly related to the effect of stimulation.

Other types of speech and voice disorders

Hypokinetic dysarthria is characterized by monotonous speech and breathy and harsh voice (Darley et al. 1969). Hypokinetic dysarthria was not only attributed to hypokinesia and rigidity of speech-related muscles but also attributed to abnormalities in sensory processing, scaling amplitude, and internal cueing (Sapir 2014). This may explain why beneficial effects of levodopa or STN-DBS on hypokinetic dysarthria are generally limited (Pinto et al. 2004). In our previous laryngoscopic study, incomplete glottal closure significantly correlated with breathy voice in PD patients and STN-DBS worsened breathy voice parallel to the aggravation of incomplete glottal closure (Tsuboi

et al. 2015b). Thus, we analyzed hypokinetic dysarthria and breathy voice separately in the present study. The incidence of stuttering at baseline (50% of PD-DBS and 45% of PD-Med) was in agreement with the reports that demonstrated the incidence of 53%–54% in PD patients (Benke et al. 2000; Goberman et al. 2010).

The incidence of stuttering and breathy voice was not significantly different between PD-DBS and PD-Med groups both at baseline and during the follow-up. After the stimulation was stopped, 22% of patients with stuttering and 33% of patients with breathy voice showed a significant improvement. Taken together, stuttering and breathy voice are thought to be mainly due to PD itself, although they can be worsened by STN-DBS in a minority of patients.

Pathophysiologies of speech and voice disorders

A majority of strained voice and spastic dysarthria appeared after increasing DBS parameters or changing active contacts. These changes are thought to result in the spread of current to the surrounding fibers. In our previous study, the analysis of electrode positions suggested a relationship between the spread of current to the corticobulbar fibers and strained voice/spastic dysarthria (Tsuboi et al. 2015b, a). There are several studies in line with this finding (Klostermann et al. 2008; Tommasi et al. 2008). However, analysis of electrode positions in the present study did not replicate our previous findings. There may be two possible reasons for this discrepancy. First, the relationship between the electrode positions and the surrounding fibers were analyzed without considering individual anatomical differences. This is a major limitation in our method. Second, strained voice and spastic dysarthria could also be related to other fibers. Several studies have suggested that speech and voice deterioration result from the spread of current to the cerebellothalamic fibers (Plaha et al. 2006; Tripoliti et al. 2011a, 2014). A recent study that employed diffusion tensor tractography reported that speech intelligibility and fluency were negatively associated with the spread of current to the cerebellothalamic fibers (Fenoy et al. 2016). In addition, a minority of strained voice and

spastic dysarthria appeared under stable or even decreased parameters. Hartmann et al. reported a decline in therapeutic impedance over time, which could lead to an unexpected spread of current (Hartmann et al. 2015). In this regard, constant-current stimulation rather than constant-voltage stimulation may be preferable.

Because the off-medication assessments were not performed, the impact of medication on speech and voice functions was unclear. Unfortunately, the impact of STN-DBS with/without medication on specific aspects of speech and voice functions (articulation, respiration, resonance, phonation, prosody, and rate control) remains inconclusive (see review in Aldridge et al. 2016). Because strained voice and spastic dysarthria are thought to be due to spread of current to the surrounding fibers, we believe the impact of medication was limited.

The basal ganglia, thalamus, cerebellum, and cerebral cortex are presumably related to the pathophysiology of stuttering. Alm suggested that the core dysfunction in stuttering is impaired ability of the basal ganglia to produce timing cues in speech (Alm 2004). STN-DBS may potentially disrupt the basal ganglia–thalamocortical network, resulting in stuttering (Burghaus et al. 2006).

The pathophysiology that STN-DBS aggravate breathy voice remains unclear. We found no correlation between the electrode positions and breathy voice. The pathophysiology could be the spread of current to the surrounding fibers or disruption of the basal ganglia–thalamocortical network. Further studies are needed to elucidate this issue.

Therapies of speech and voice disorders

Speech and voice disorders reduce the quality of life of patients and can discourage social activity. In our experience, severe and long-standing strained voice or spastic dysarthria tends to remain to a varying extent after optimal stimulation adjustment. This may be due to disease progression and/or plasticity changes induced by long-term STN stimulation. An improved understanding of the types of speech and voice disorders may lead to early intervention.

Lee Silverman Voice Treatment (LSVT LOUD) and other behavioral treatments may be effective for hypokinetic dysarthria (Atkinson-Clement et al. 2015).

As strained voice and spastic dysarthria are thought to be related to the spread of current to the surrounding fibers, strategies that reduce the current spread are reasonable. Picillo et al. recently reported practical and comprehensive programming strategies (Picillo et al. 2016). At first, it is recommended to turn off each side alternatively to understand if speech and voice disorders are related to one side stimulation or to the combination of both sides. Then, voltage reduction, switching to bipolar stimulation, and switching to interleaving stimulation should be tried step by step. Although low-frequency stimulation (e.g. 60 Hz) can be an option, it is often intolerable because of worsening of motor symptoms (di Biase and Fasano 2016). If speech and voice disorders cannot be avoided because of suboptimally placed electrodes, repositioning of the electrodes should be considered.

If we notice that STN-DBS worsen stuttering or breathy voice, reprogramming can be tried. However, there is no established programming strategies for these disorders. External cues such as pacing boards can alleviate stuttering in PD patients treated with STN-DBS (Suzuki et al. 2013).

Limitations

First, the number of PD-Med patients was relatively small and selection bias could exist. Although age, age at onset, sex, and speech/voice, motor, and cognitive functions were not significantly different between the two groups, PD-Med group had less motor complications and lower LEDD than PD-DBS group. The differences in patient characteristics should be carefully considered. However, LEDD at 1 year was not significantly different between groups; all the patients were assessed in the on-state; and the incidence of hypokinetic dysarthria, stuttering, and breathy voice was not significantly different between the two groups throughout the follow-up period. Considering these facts, the speech and voice functions of the two groups are thought to be

comparable.

Second, as mentioned above, the off-medication assessment was not performed. Third, we did not assess individual differences in anatomical structures, including the surrounding fibers of STN. Future studies using diffusion tensor tractography should clarify the differences in the types of speech and voice disorders among responsible fibers. Finally, the off-stimulation assessment was performed 30 min after the stimulation was stopped. Although we observed specific degrees of changes in speech and voice functions, the residual DBS effects need to be considered.

Conclusions

Approximately 90% of PD patients had one or more types of speech and voice disorders (hypokinetic dysarthria, breathy voice, and stuttering) before surgery, which stemmed from PD itself. A slight but significant speech and voice deterioration was observed in PD-DBS group during the 1-year follow-up. Strained voice and spastic dysarthria were the most common DBS-induced speech and voice disorders. Although Stuttering and breathy voice may be mainly due to PD itself, they can be worsened by STN-DBS in a minority of patients. An improved understanding of these speech and voice disorders may be useful when detecting DBS-induced speech and voice disorders during the early phase. To improve the quality of life of patients, further clarification of the underlying pathophysiologies and advances in treatment strategy are needed.

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Conflicts of interest

Nothing to report.

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Table 1. Patient characteristics of PD-DBS and PD-Med groups

	PD-DBS (n = 32)		PD-Med (n = 11)	
	Baseline	1 year	Baseline	1 year
Age (years)	63.3 ± 9.1		68.1 ± 4.6	
Age at onset (years)	51.9 ± 9.6		53 ± 5.0	
Sex (female, %)	59.4		45.5	
UPDRS-III	14.6 ± 7.3	13.7 ± 8.2	18.9 ± 8.0	19 ± 9.0
UPDRS-IV	7.1 ± 3.3*	3.3 ± 3.2*†	3.9 ± 2.2	4.2 ± 1.7
MMSE	27.7 ± 2.2	28.0 ± 2.1	26.9 ± 3.0	27.0 ± 3.7
MoCA	23.9 ± 3.3	23.9 ± 4.0	24.0 ± 5.8	23.7 ± 4.5
LEDD (mg)	952.0 ± 371.9*	686.3 ± 362.9*†	645.6 ± 117.3	727.9 ± 226.0†

Values are mean ± SD. P value <0.05 was considered significant. * Significant differences between two groups. † Significant longitudinal changes within group. PD-DBS = patients treated with deep brain stimulation; PD-Med = medically treated patients; UPDRS = Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; LEDD = levodopa equivalent daily dose.

Table 2. DBS settings

	3 months	6 months	12 months
Monopolar/ Bipolar: left (n)	30 / 2	30 / 2	30 / 2
Amplitude: left (V)	1.8 ± 0.5	1.9 ± 0.5	2.0 ± 0.4
Frequency: left (Hz)	133.6 ± 11.4	131.6 ± 8.8	134.1 ± 9.8
Pulse width: left (µs)	61.9 ± 7.5	63.8 ± 10.1	69.4 ± 14.1
Monopolar/ Bipolar: right (n)	30 / 2	30 / 2	30 / 2
Amplitude: right (V)	1.8 ± 0.5	2.0 ± 0.4	2.1 ± 0.4
Frequency: right (Hz)	133.6 ± 11.4	131.6 ± 8.8	134.1 ± 9.8
Pulse width: right (µs)	61.9 ± 7.5	63.8 ± 10.1	68.4 ± 13.7

Table 3. Speech and voice functions of PD-DBS and PD-Med groups

	PD-DBS (n = 32)			PD-Med (n = 11)	
	Baseline	1 year DBS on	1 year DBS off	Baseline	1 year
AMSD					
overall severity of speech disorders					
Intelligibility	1.5 ± 0.6	1.9 ± 0.6†	1.8 ± 0.4	1.6 ± 0.5	1.7 ± 0.4
Naturalness	2.3 ± 0.8	2.8 ± 0.9†	2.5 ± 0.7	2.3 ± 0.8	2.5 ± 0.8
Subparts					
Imprecise consonants	0.3 ± 0.5	0.9 ± 0.7†‡	0.5 ± 0.5	0.4 ± 0.5	0.5 ± 0.5
Monoloudness	0.8 ± 0.9	1.0 ± 0.8	1.1 ± 0.7	1.3 ± 0.6	1.0 ± 0.6
Monopitch	0.8 ± 0.8	1.0 ± 0.8	1.0 ± 0.7	1.3 ± 0.6	0.8 ± 0.4†
Low volume	0.5 ± 0.6	0.8 ± 0.9†‡	0.9 ± 0.8	1.1 ± 0.8	0.6 ± 0.7
Short rushes of speech	0.3 ± 0.5	0.4 ± 0.8	0.3 ± 0.5	0.3 ± 0.5	0.5 ± 0.7
Voice tremor	0.7 ± 0.6	0.6 ± 0.6	0.7 ± 0.7	0.5 ± 0.7	0.8 ± 0.4
Sound repeated	0.6 ± 0.6	0.8 ± 0.8†	0.6 ± 0.7	1.0 ± 0.9	1.4 ± 0.9†
Hypernasality	0.4 ± 0.6	0.9 ± 0.8†	0.6 ± 0.6	0.3 ± 0.5	0.5 ± 0.5
Abnormal rate	0.7 ± 0.8	1.0 ± 0.8†	0.8 ± 0.7	0.6 ± 0.7	1.0 ± 0.8†
Variable rate	1.0± 0.7	1.4 ± 0.7†‡	0.8 ± 0.5	1.0 ± 0.6	1.2 ± 1.0
Excess loudness variation	0.9 ± 0.7	1.2 ± 0.8‡	0.8 ± 0.6	0.9 ± 0.3	0.9 ± 0.5
Abnormal pitch level	0.7 ± 0.6	1.0 ± 0.7	0.7 ± 0.7	0.3 ± 0.5	0.7 ± 0.5†
Variable pitch	0.3 ± 0.5	0.5 ± 0.6	0.3 ± 0.5	0.3 ± 0.5	0.5 ± 0.5
GRBAS scale					
overall severity of voice disorders					
Grade of dysphonia	1.2 ± 0.4	1.6 ± 0.6*†	1.3 ± 0.5	1.1 ± 0.3	1.1 ± 0.3
Subparts					
Roughness	0.8 ± 0.7	1.4 ± 0.6†‡	1.0 ± 0.7	0.9 ± 0.6	1.1 ± 0.3
Breathiness	0.8 ± 0.7	1.0 ± 0.8	0.8 ± 0.7	0.9 ± 0.5	0.9 ± 0.5
Asthenia	0.6 ± 0.7	0.9 ± 0.8†	0.8 ± 0.8	0.6 ± 0.6	0.6 ± 0.7
Strain	0.3 ± 0.6	0.8 ± 0.6*†‡	0.3 ± 0.5	0.3 ± 0.5	0.2 ± 0.4

Values are mean ± SD. P value <0.05 was considered significant. * Significant differences between the two groups. † Significant longitudinal changes within groups. ‡ Significant difference between the on- and off-stimulation conditions. PD-DBS = patients treated with deep brain stimulation; PD-Med = medically treated patients; AMSD = Assessment of Motor Speech for Dysarthria; GRBAS scale = Grade of dysphonia, Roughness,

Breathiness, Asthenia and Strain scale.

Table 4. Changes of the types of speech and voice disorders in PD-DBS and PD-Med groups

	Baseline types		Additional types		Significant improvement after stopping stimulation
	PD-DBS	PD-Med	PD-DBS	PD-Med	
Hypokinetic dysarthria	20 (63%)	9 (82%)	0 (0%)	0 (0%)	0/20 (0%)
Stuttering	16 (50%)	5 (45%)	3 (9%)	2 (18%)	4/18 (22%)
Breathy voice	21 (66%)	8 (73%)	4 (13%)	1 (9%)	8/24 (33%)
Strained voice	1 (3%)	1 (9%)	9 (28%)	0 (0%)	7/9 (78%)
Spastic dysarthria	0 (0%)	0 (0%)	14 (44%) *	0 (0%)	8/13 (62%)

The column of "baseline types" provides n (%) of specific types of speech and voice disorders at baseline. The column of "additional types" provides n (%) of types of speech and voice disorders which patients developed during the 1-year follow-up. P value <0.05 was considered significant. * Significant differences between two groups. The column of "Significant improvement after stopping stimulation" provides the number of patients and the percentage whose speech and voice disorders significantly improved after stopping stimulation.

Figure legends

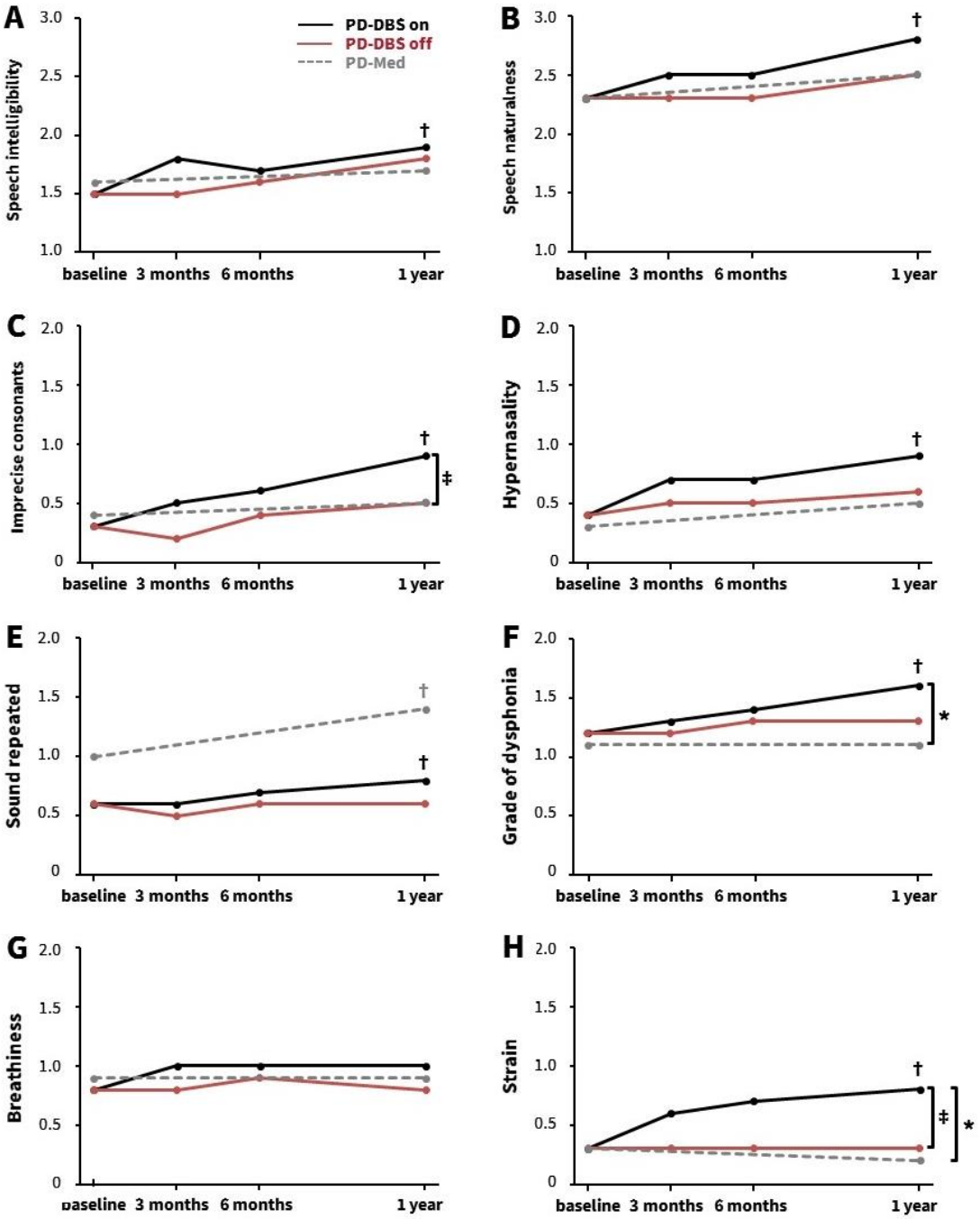

FIG. 1. (A) Speech intelligibility, (B) speech naturalness, (C) imprecise consonants, (D) hypernasality, (E) sound repeated, (F) grade of dysphonia, (G) breathiness, and (H) strain at baseline and at 3 months, 6 months, and 1 year after surgery. Black solid lines represent PD-DBS group in the on-stimulation conditions; red solid lines represent PD-DBS group in the off-stimulation conditions; and gray dotted lines represent PD-Med group. *Significant differences between the two groups. † Significant longitudinal changes within group. ‡Significant differences between the on- and off-stimulation conditions.

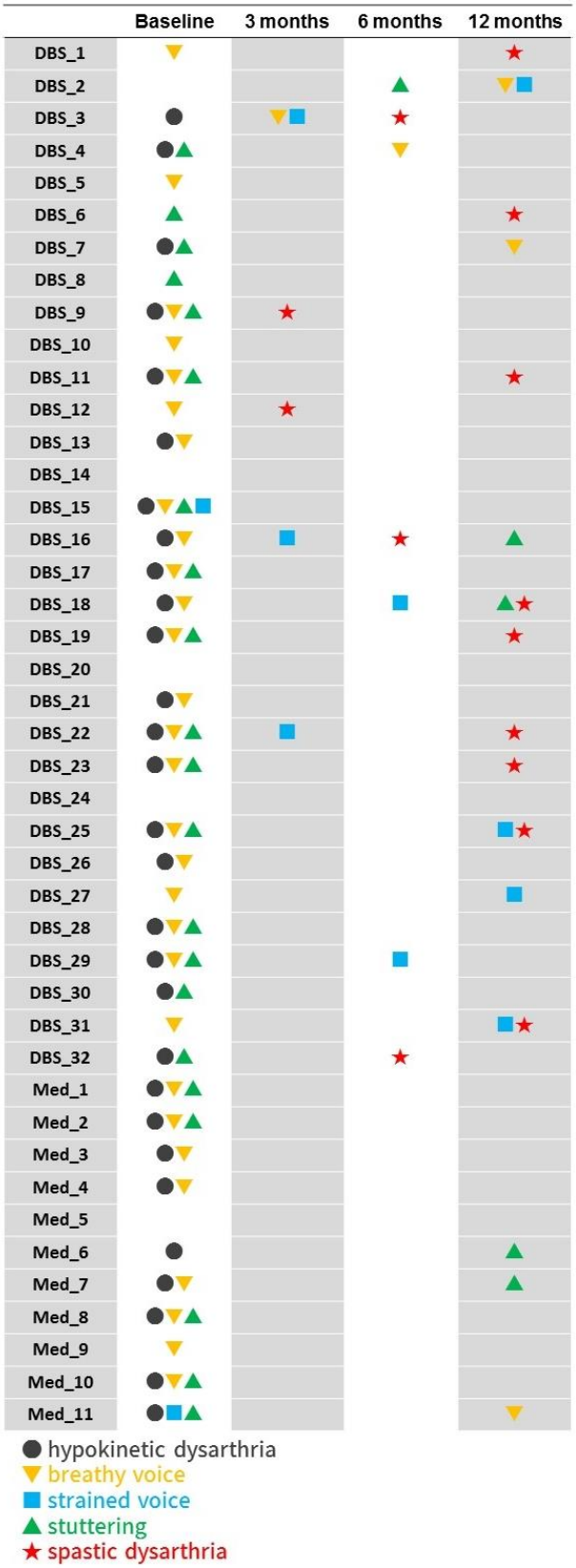

FIG. 2. Longitudinal changes in the types of speech and voice disorders in 32 PD patients treated with STN-DBS and 11 PD patients treated with medication. The types of disorders of patients are shown in each row. The types of disorders at baseline are shown in the "Baseline" column. The additional types of disorders at 3, 6, and 12 months are shown in the "3 months", "6 months", and "12 months" columns, respectively. Black circles indicate hypokinetic dysarthria; yellow triangles indicate breathy voice; blue squares indicate strained voice; green triangles indicate stuttering; and red stars indicate spastic dysarthria.

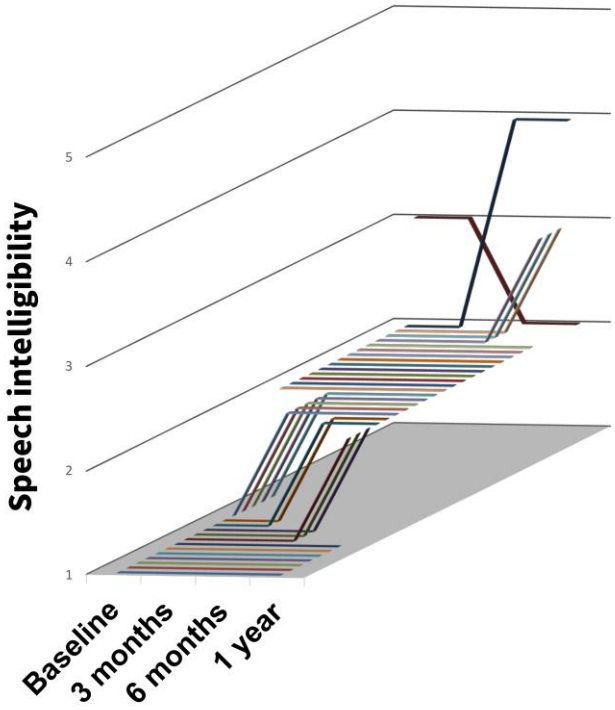

FIG. 3. Changes in overall speech intelligibility of 32 PD patients treated with STN-DBS. The colored lines show changes in speech intelligibility in each patient. Score is defined as 1 = fairly understandable; 2 = understandable in large part, but with some difficulty; 3=understandable if the listener knows the content spoken; 4=understandable in small part; 5 = not understandable at all.