JSLHR

Research Article

The Effect of Deep Brain Stimulation on the Speech Motor System

Doris Mücke,[a] Johannes Becker,[a,b] Michael T. Barbe,[b,c] Ingo Meister,[b] Lena Liebhart,[b] Timo B. Roettger,[a] Till Dembek,[b] Lars Timmermann,[b] and Martine Grice[a]

Purpose: Chronic deep brain stimulation of the nucleus ventralis intermedius is an effective treatment for individuals with medication-resistant essential tremor. However, these individuals report that stimulation has a deleterious effect on their speech. The present study investigates one important factor leading to these effects: the coordination of oral and glottal articulation.
Method: Sixteen native-speaking German adults with essential tremor, between 26 and 86 years old, with and without chronic deep brain stimulation of the nucleus ventralis intermedius and 12 healthy, age-matched subjects were recorded performing a fast syllable repetition task (/papapa, tatata, kakaka/). Syllable duration and voicing-to-syllable ratio as well as parameters related directly to consonant production, voicing during constriction, and frication during constriction were measured.
Results: Voicing during constriction was greater in subjects with essential tremor than in controls, indicating a perseveration of voicing into the voiceless consonant. Stimulation led to fewer voiceless intervals (voicing-to-syllable ratio), indicating a reduced degree of glottal abduction during the entire syllable cycle. Stimulation also induced incomplete oral closures (frication during constriction), indicating imprecise oral articulation.
Conclusion: The detrimental effect of stimulation on the speech motor system can be quantified using acoustic measures at the subsyllabic level.

Key Words: dysarthria, speech production, articulation, neurologic disorders, speech motor control

In this study, we investigate the effect of chronic deep brain stimulation (DBS) of the nucleus ventralis intermedius (VIM) on the production of speech in individuals with essential tremor.[1] VIM-DBS is performed to suppress medically resistant tremor, especially for essential tremor and tremor-dominant Parkinson's disease (Benabid et al., 1996). VIM is regarded as a relay station in the tremor network connecting cerebellum and motor cortex (Schnitzler, Munks, Butz, Timmermann, & Gross, 2009) and is, therefore, the classical neuroanatomical target for DBS in essential tremor. VIM-DBS is a highly effective treatment (Flora, Perera, Cameron, & Maddern, 2010) and usually leads to a tremor reduction of 60–80% (Benabid et al., 1996).

[a]Institut für Linguistik—Phonetik, University of Cologne, Cologne, Germany
[b]Department of Neurology, University Hospital Cologne, Cologne, Germany
[c]Cognitive Neurology Section, Institute of Neurosciences and Medicine (INM-3), Research Centre Juelich, Juelich, Germany
Correspondence to Doris Mücke: doris.muecke@uni-koeln.de

Editor: Jody Kreiman
Associate Editor: Julie Liss
Received June 20, 2013
Revision received December 3, 2013
Accepted December 28, 2013
DOI: 10.1044/2014_JSLHR-S-13-0155

[1]Essential tremor is the most common movement disorder, usually presenting clinically with symmetrical onset of postural and/or intention tremor of the upper limb, sometimes affecting other body parts such as head, voice, or trunk (Deuschl & Elble, 2009). The pathophysiology of essential tremor is unknown. Some studies support the idea that abnormal motor unit entrainment at frequencies of 4–12 Hz emerges from pathological oscillation in the corticobulbocerebellothalamocortical loop (Elble, 2013). This pathological network has been described as the tremor network (Raethjen & Deuschl, 2012). For years, essential tremor has been regarded as a benign disorder. However, in the recent literature there is growing evidence from post mortem studies that neuropathological changes such as Lewy bodies or loss of Purkinje cells underlie essential tremor pathogenesis (Louis, 2009), though other studies have not supported this finding (Rajput, Adler, Shill, & Rajput, 2012). Since essential tremor can be associated with cerebellar symptoms, cognitive defects, and dystonia, Elble (2013) recently raised the question as to whether essential tremor should be regarded as a clinical syndrome rather than a monosymptomatic disease and proposed a broader definition of essential tremor.

Disclosure: *The authors have declared that no competing interests existed at the time of publication.*

FN2 However, stimulation-induced dysarthria[2], p. 142). is a common side effect of thalamic/subthalamic stimulation (Flora et al., 2010; Krack et al., 2002) and, as a result, the extent to which tremor can be suppressed in individuals with essential tremor is limited, as suboptimal parameter settings just below the threshold inducing dysarthria have to be selected by the treating clinician. Recent analyses in controlled essential tremor studies indeed demonstrated that dysarthria is the most significant adverse event, affecting individuals with essential tremor (values reported in the literature range from almost 9% found in Flora et al., 2010, to 75% found in Pahwa et al., 2006) and inducing a severe effect on quality of life and social functioning. Individuals with essential tremor report that the deterioration in speech resembles slurred speech after alcohol consumption.

VIM-DBS-induced dysarthria has been investigated for individuals with essential tremor. Kronenbuerger et al. (2009) used a fast syllable repetition task taking acoustic syllable durations as the relevant measure, a production parameter that is commonly used when investigating articulation rate (Crystal & House, 1990). They selected this measure because slowing down of articulation rate is a common feature of various forms of dysarthria (Ackermann, Hertrich, & Hehr, 1995; Kent, Kent, Weismer, & Duffy, 2000; Ziegler, 2002). They used consonant–vowel sequences (CV) with voiced stops (/bababa/, /dadada/, and /gagaga/). Compared to a healthy control group, individuals of the essential tremor group with additional signs of cerebellar dysfunctions showed longer syllable durations. However, no difference in syllable durations was found when comparing the on-DBS condition (activated stimulation) and off-DBS condition (inactivated stimulation). The authors therefore concluded that, in their study, VIM-DBS had no discernible effect on the speech motor system.

Pützer, Barry, and Moringlane (2007) also studied the effect on articulation of VIM-DBS, but this time in individuals suffering from tremor caused by multiple sclerosis. Unlike Kronenbuerger et al. (2009), they reported on discernable effects of stimulation on the speech motor system. They focused on the coordination of the oral and glottal control mechanisms in the production of syllables and carried out a fast syllable repetition task with sequences containing voiceless stops (/papapa/, /tatata/, and /kakaka/). Their motivation to include voiceless rather than voiced stops was that the alternation of voiceless stop and voiced vowel enabled a more detailed analysis of the coordination of the glottal and oral subsystems. When comparing productions with activated and inactivated stimulation (on-DBS and off-DBS conditions), they (like Kronenbuerger et al., 2009) found no change in articulation rate operationalized through syllable duration, but they did find differences at the subsyllabic level, namely, during the stop consonant: (a) aperiodic energy due to incomplete oral closure and (b) periodic energy due to ongoing vocal fold vibration. They further found (c) shorter voiceless intervals under stimulation, due to insufficient glottal abduction, indicating reduced voicing control.

The present study investigates whether deterioration reported by the individuals with essential tremor under stimulation can be operationalized in the acoustic dimension. We compare the productions of a control group and individuals of the essential tremor group with inactivated stimulations[3] and within-subject productions with activated and inactivated stimulation. Therefore, we provide a clearly defined and reliable set of four observer-independent acoustic measures for capturing impairments of the oral-glottal control related to dysarthria: (1) syllable duration, (2) voicing-to-syllable ratio, (3) voicing during constriction, and (4) frication during constriction (see Table 1). The first measure is related to articulation rate. Slowness in articulation is regarded as a feature of dysarthria (Ackermann et al., 1995; Kent et al., 2000; Ziegler, 2002). The second measure is related to glottal control, where insufficient glottal abduction is regarded as a sign of dysarthria (Ackermann & Ziegler, 1989; Weismer & Martin, 1992; Ziegler & von Cramon, 1987). The last two measures are both related to deficits in the production of stop consonants. Kent, Weismer, Kent, Vorperian, and Duffy (1999) claimed:

FN3 T1

> The precision of stop consonant production can be determined in part by measures of the acoustic energy during the intended occlusive phase, or stop gap. . . . In general, normal production of a voiceless stop consonant is associated with a virtually silent gap. But some dysarthric speakers . . . tend to produce energy during the gap. This energy is typically one of two forms: turbulence noise (spirantization) generated at the site of oral constriction because an incomplete occlusion, and voicing energy, which often occurs because of poor coordination between laryngeal and supralaryngeal actions. (Kent et al., 1999, pp. 157–158)

[2]Clinically, dysarthria is defined as "a defect in articulation with intact mental functions and comprehension of spoken and written language and normal syntax [. . .] This is a pure motor disorder of the muscles of articulation" (Victor & Ropper, 2001, p. 504). Compare also Raphael, Borden, and Harris (2011, p. 313): "A disorder of articulation caused by the impairment of parts of the nervous system that control the muscles of articulation." Dysarthria can affect more than one articulatory subsystem: "[T]he disruption may be distributed over components in the respiratory, laryngeal and supralaryngeal articulatory subsystems" (Kent et al., 1999

[3]In comparison to healthy control subjects, individuals diagnosed with essential tremor not treated with DBS already show deterioration in speech and swallowing. The literature reports disturbances in supralaryngeal articulation (Kronenbuerger et al., 2009), slower esophageal transit times (Blonsky, Logemann, Boshes, & Fisher, 1975), and voice tremor (Blonsky et al., 1975; Carpenter et al., 1998; Gamboa et al., 1998; Putzke et al. 2005). In the present study, we compare the control group with subjects of the essential tremor group with inactivated stimulation, assuming that the latter relates to the preoperative state.

Table 1. Measurement variables, definitions, and indications in dysarthric speech.

Measure	Definition of the measure	Parameter in dysarthric speech
Syllable duration (ms)	Duration of the entire syllable cycle defined as the time from the onset of the consonantal constriction to the offset of the following vowel (substantial decrease in the amplitudes of the second vowel formant, F2).	Describes the overall articulation rate in the syllable repetition task. Slowing down the articulation rate in terms of prolonged syllables is described as an indicator for various forms of dysarthria (Ackermann et al., 1995; Kent et al., 2000; Ziegler, 2002).
Voicing- to-syllable ratio (%)	Defined as the duration of all voiced portions in relation to the duration of the entire syllable cycle (measure 1). The voiced portions include two components: the duration of the vowel (defined from a substantial increase to a drop in energy of F2) and the potentially voiced parts during the consonant (defined as low frequency periodic structure above 500 Hz where voicing continues into the constriction phase).	Describes phonation during the entire syllable cycle including all voiced parts during the vowel and consonant production. Voicing perseveration can be attributed to insufficient glottal abduction in dysarthric speech (e.g., cerebral palsy [Farmer, 1980], Parkinson's disease [Ackermann & Ziegler, 1989; Ziegler & von Cramon, 1987], or multiple sclerosis [Kent et al., 1999; Kent et al., 2000; Pützer et al., 2007; Weismer & Martin, 1992]), a sign of disturbances in voicing control.
Voicing during constriction (%)	Defined as the frequency of occurrence of voicing energy continuing longer than 20 ms during the production of the consonantal constriction (binary, measurements adapted from Weismer, 1984, p. 105).	Ongoing vocal fold vibrations during the voiceless constriction indicate poor coordination of the laryngeal and supralaryngeal systems, and is described in the relevant literature as an indicator for dysarthria (Parkinson's disease [Weismer 1984; Ackermann & Ziegler, 1991] and multiple sclerosis [Kent et al., 1999; Pützer et al., 2007]), reflecting problems in activating laryngeal devoicing actions. Ongoing vocal fold vibrations are caused by articulatory impairment of the larynx in dysarthric speakers, shifting voiceless stops in the direction of voiced stops. Thus "voicing information may not be transmitted well by dysarthric speakers" (Weismer & Martin, 1992, p. 88).
Frication during constriction (%)	Defined as the frequency of occurrence of aperiodic energy/turbulent noise during the production of the intended consonantal constriction (binary).	Indicates imprecise articulation of the stop consonant. The aperiodic energy is caused by leaking or incomplete closure in the oral tract and can be interpreted as a sign of dysarthria (Parkinson's disease [Ackermann et al., 1995; Kent et al., 1999; Logemann & Fisher, 1981; Schweitzer, 2005; Weismer, 1984]; ataxic dysarthria [Kent & Rosenbek, 1982]; multiple sclerosis [Pützer et al., 2007]; and traumatic brain injury [Ziegler & von Cramon, 1983]).

We hypothesized that, in the speech production of individuals with essential tremor, we would find a deterioration in coordination of the glottal and oral systems and incomplete oral closure when DBS was applied.

Method

Ethics

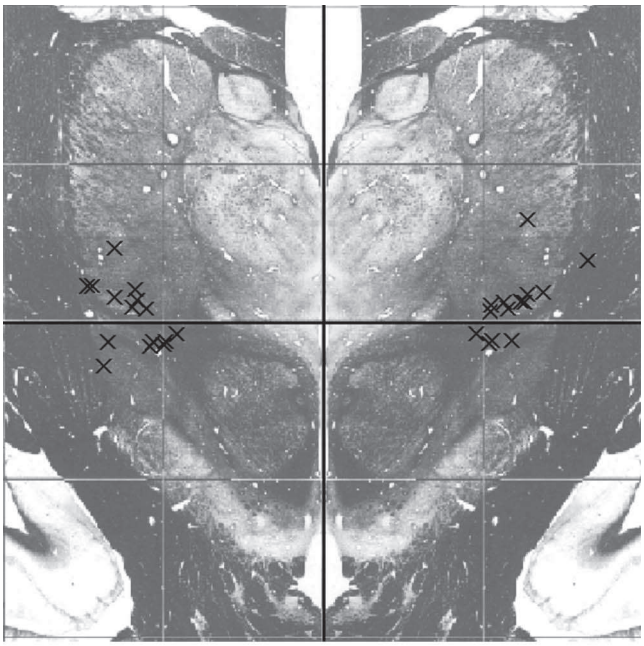
This study was approved by the Local Ethics Committee of the University of Cologne (Study No. 08–269). Each participant with essential tremor gave written informed consent before study participation. Research was conducted in accordance with the Declaration of Helsinki. Control subjects provided informed consent.

Participants

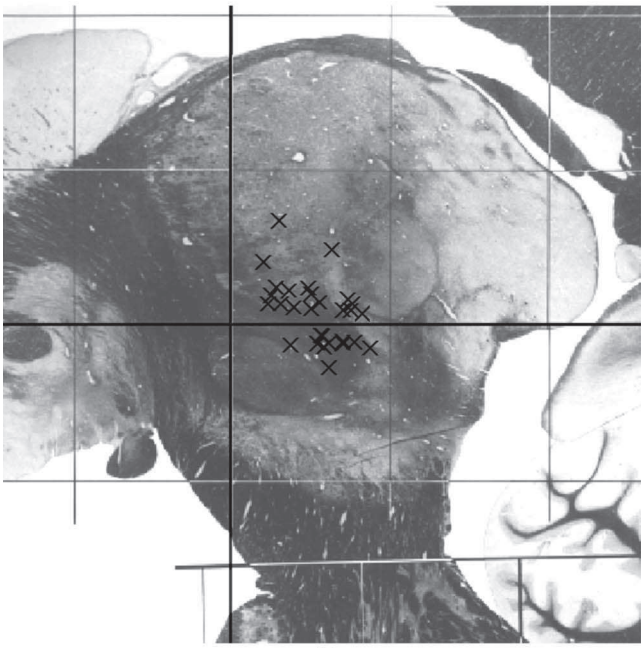
Sixteen native-speaking German individuals with essential tremor between 26 and 86 years old (M = 64.69, SD = 14.87; 12 male, 4 female) participated in our study. Fourteen of them had been bilaterally and 2 of them had been unilaterally (only left) implanted with a DBS system in the VIM at least 3 months before the recordings took place (between March and August 2009; for standard brain coordinates of all electrode contacts, see Figure 1). F1

The exact localization of the electrodes was confirmed via stereotactic X-ray or CCT for each single individual with essential tremor and projection of the image on the preoperative magnetic resonance imaging. The mean stereotactic coordinates (±SD) from 30 electrodes

Figure 1. For visualization, standard brain coordinates of active electrode contacts were plotted on coronal (A) and sagittal (B) sections of the Brain Atlas of Schaltenbrand and Wahren (Nowinski & Belov, 2003). The center of each electrode contact is indicated by an X. In case two or more electrode contacts were activated, the most ventral was plotted on the image. All electrode contacts are located in the nucleus ventralis intermedius (VIM) of the thalamus and, in some cases, in the posterior subthalamic area (PSA) as well.



(a)



(b)

for all 16 individuals with essential tremor are shown in Table 2. **T2**

All contacts were located in the VIM or in the region more ventral to the VIM, the so-called posterior subthalamic area (PSA). Chronic DBS in the PSA is known to have a similar or even better tremor-suppressing effect in individuals with essential tremor (Barbe et al., 2011).

None of the individuals with essential tremor was diagnosed with preoperative dysarthria. All individuals with essential tremor were operated as described in Barbe et al. (2011). They were not specifically selected (i.e., stimulation-induced dysarthria after DBS was not an inclusion criterion), and all individuals with essential tremor were tested while on and off VIM stimulation. Before off testing, VIM-DBS was paused for at least 1 hr. The individual stimulation parameters of each subject with essential tremor were used in the on-stimulation condition. All DBS parameters were optimized before the recordings to achieve best tremor suppression and subjectively smallest side effects. In general, DBS settings were set to monopolar (case positive, at least one electrode contact negative), with an amplitude between 1.0 and 4.4 V, pulse width of 60–90 μs, and a stimulation frequency of 125–180 Hz. A detailed table with the stimulation parameters for each subject with essential tremor is shown in the Appendix.

The control group comprised 12 age-matched and healthy German native speakers (8 male, 4 female), 44 to 85 years old (M = 66.75, SD = 16.34). An unpaired t test confirmed that the control group did not differ significantly from the essential tremor group in age, $t(26) = -.348$, $p = .73$. For the comparison of this study to previous studies, it is important to stress that the control group was matched for age. This was not the case, for example, in Pützer et al. (2007), whose in the control group subjects were younger than those in the group of individuals with multiple sclerosis.

Recordings and Speech Materials

The participants were recorded acoustically using a Marantz PMD 670 digital audio recorder and an AKG C520 headset condenser microphone. With the use of a headset microphone, a mouth-to-microphone distance of approximately 5 cm could be kept constant independently of the participant's head movement. The acoustic signal was converted to 44.1 kHz/16 bit. All recordings took place at the Department of Neurology of the University Hospital Cologne.

For each of the subjects with essential tremor, two separate recording sessions were carried out (on and off stimulation; the latter defined as at least 1 hr after deactivation). In each session, we recorded a fast syllable repetition task, a standard task in which speakers were instructed to produce a given syllable as quickly and as often as possible in one single breath (/papapa/, /tatata/, or /kakaka/). The task was demonstrated by the examiner before the beginning of the first recording.

Table 2. Stereotactic coordinates from 30 electrodes implanted in the right and left nucleus ventralis intermedius (VIM) with reference to the midcommissural point.

Hemisphere	*n*	*x*-coordinate	*y*-coordinate	*z*-coordinate
VIM left hemisphere	16	–12.01 ± 1.73	–5.9 ± 1.46	0.43 ± 2.02
VIM right hemisphere	14	11.95 ± 1.79	–5.04 ± 2.29	1.18 ± 2.09

Note. Values in millimeters are shown as means ± *SD*.

Across all data, an average of 44 syllable repetitions were produced on a single breath per trial (controls: 49 syllable repetitions; subjects with essential tremor, off-DBS state: 42 syllable repetitions; on-DBS state: 39 syl- FN4 lable repetitions).[4]

Labeling and Measures

For analysis, we selected 10 subsequent CV sequences from each /papapa/, /tatata/, and /kakaka/ sequence. To avoid durational effects associated with prosodic boundaries (such as utterance initial/final strengthening and lengthening, which have been shown to mark edges of prosodic domains; see, e.g., Fougeron & Keating, 1997), the first and last three repetitions were excluded from the analysis.

For the subjects with essential tremor, there were 960 target syllables in total (16 speakers × 3 places of articulation × 10 repetitions × 2 stimulation states). We discarded a total of 40 target syllables from the analysis, including two sets of alveolar sequences (on and off, one speaker), as well as two sets of velar ones (on and off, one speaker) because different stress patterns were used (weak-weak-strong as opposed to a pattern without prominent stress marking as emphasized by the instructions).

For the control subjects, there were 360 target syllables (12 speakers × 3 places of articulation × 10 repetitions). We included a total of 1,280 target syllables (subjects with essential tremor and controls together) in the final analysis.

All data were displayed and labeled by hand in PRAAT (Boersma & Weenink, 2010) by Johannes Becker. To check for consistency in annotation, a subset of 10% of the corpus was labeled by an independent annotator, who was blind to all conditions. The subset consists of one syllable per trial (/pa/, /ta/, and /ka/, respectively, for each speaker and stimulation condition).

We tested the interrater reliability by calculating the intraclass coefficient (ICC; Fleiss & Cohen, 1973) for continuous variables (syllable duration, voicing-to-syllable ratio) and Cohen's kappa (Cohen, 1960) for binomial variables (voicing during constriction, frication during constriction) using the R package irr (Gamer, Lemon, & Singh, 2012). We found a high degree of interrater reliability in all measures. For all continuous variables, the ICC value was very high (i.e., above .9). For the binomial variables, presence of frication achieved a kappa value of .75, and the presence of voicing achieved a kappa value of .83.

Annotations were carried out using the speech waveform and a wide-band spectrogram. Figure 2 provides an F2 example of 10 repetitions of the syllable /ka/, illustrating the type of variation obtained in the acoustic signal, especially during consonant production. The duration-related variables reported later were used (cf. Table 1).

Figure 3 presents an example for /ka/ production F3 without articulatory disturbances. During the constriction of the stop consonant, the air stream is interrupted (a silent energy gap between landmarks 1 and 2), followed by the release and aspiration (2–3) and the vowel (3–4).

Figures 4 and 5 display examples of /ka/ production F4 F5 with articulatory disturbances during the consonantal constriction: Figure 4 shows frication in terms of aperiodic energy during the constriction (label 1–2). While a tight articulatory closure results in a silent gap on the acoustic surface, a leaking closure leads to the aerodynamic consequence of turbulence in the partially blocked air flow. Figure 5 shows frication in combination with voicing during constriction (label 1–2). The low-frequency periodic energy during the closure is a result of ongoing vocal fold vibrations during the oral stop closure.

When the articulation is affected, we predict the following deviations common for dysarthria (cf. Table 2):

[4]When looking at the healthy control group, the syllables per second differ from those reported in the literature. Instead of producing around 5.5 to seven syllables per second (Kent et al., 1987), our group produced an average of five syllables per second. There might be several reasons for this: First, the average age of the subjects in our control group is rather high. Our subjects were, on average, 29 years older compared to, for example, Pützer et al.'s subjects (2007, p. 742), and elderly adults tend to produce higher syllable durations in fast syllable repetition tasks than younger adults (Devadiga & Bhat, 2012). Second, the speech material differs in the fast syllable repetition tasks used in the literature. For example, Kronenbuerger et al. (2009) used fully voiced sequences such as /bababa/, /dadada/, /gagaga/, or even /nanana/, which requires less effort for the glottis and decreases the difficulty of the sequence (Kingston & Diehl, 1994). Kent, Kent, and Rosenbek (1987) reported that the most commonly selected monosyllabic triads for fast syllable repetition tasks are /pV/, /tV/, and /kV/, containing a more centralized vowel, where the distance for the tongue and jaw to travel is shorter compared to low vowels. Other studies even used syllables containing a full centralized vowel, /p@/, /t@/, /k@/ (Yang, Chung, Chi, Chen, & Wang, 2011) or alternated the place of articulation by using polysyllabic triades such as /pVtVkV/ (Konstantopoulos, Charalambous, & Verhoeven, 2011) and /badaga/ (Kronenbuerger et al., 2009), allowing for a higher degree of articulatory overlap.

Figure 2. Acoustic waveform and spectrogram of 10 syllable repetitions for the syllable /ka/, participant of the essential tremor group (on-DBS condition). DBS = deep brains stimulation.

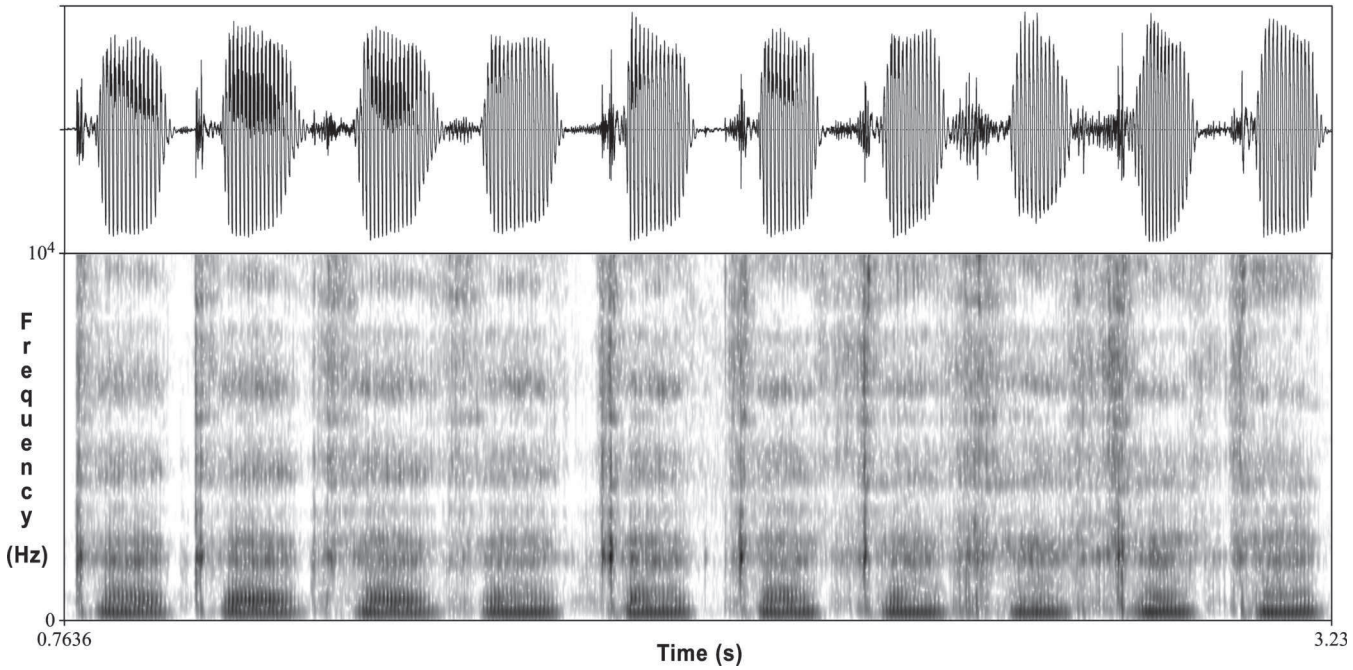


Figure 3. Labeling scheme for one syllable cycle /ka/ with acoustic waveform and spectrogram taken from the control group. Landmarks: 1 = onset of consonantal constriction, 2 = onset of release and aspiration, 3 = onset of vowel, 4 = offset of vowel. Production without articulatory disturbances. C = consonant; V = vowel.

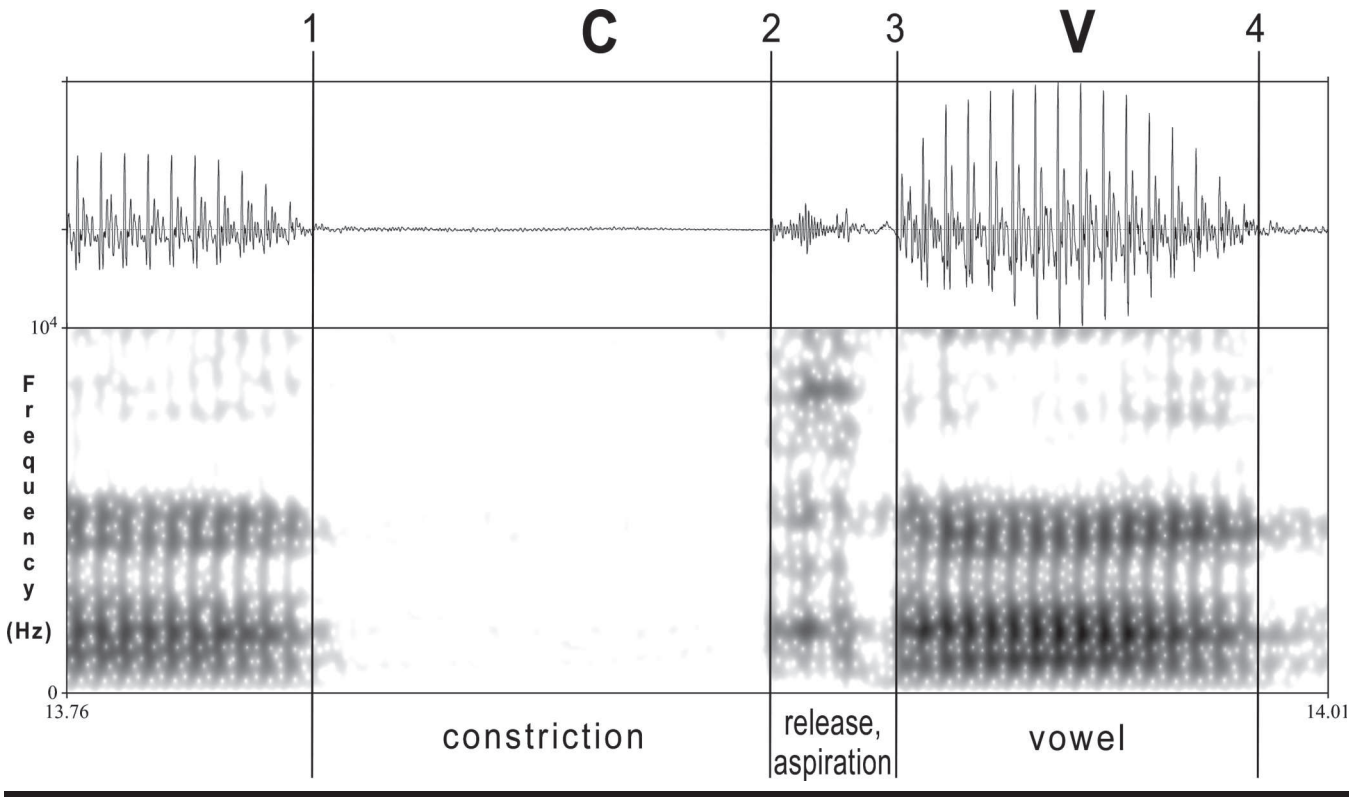
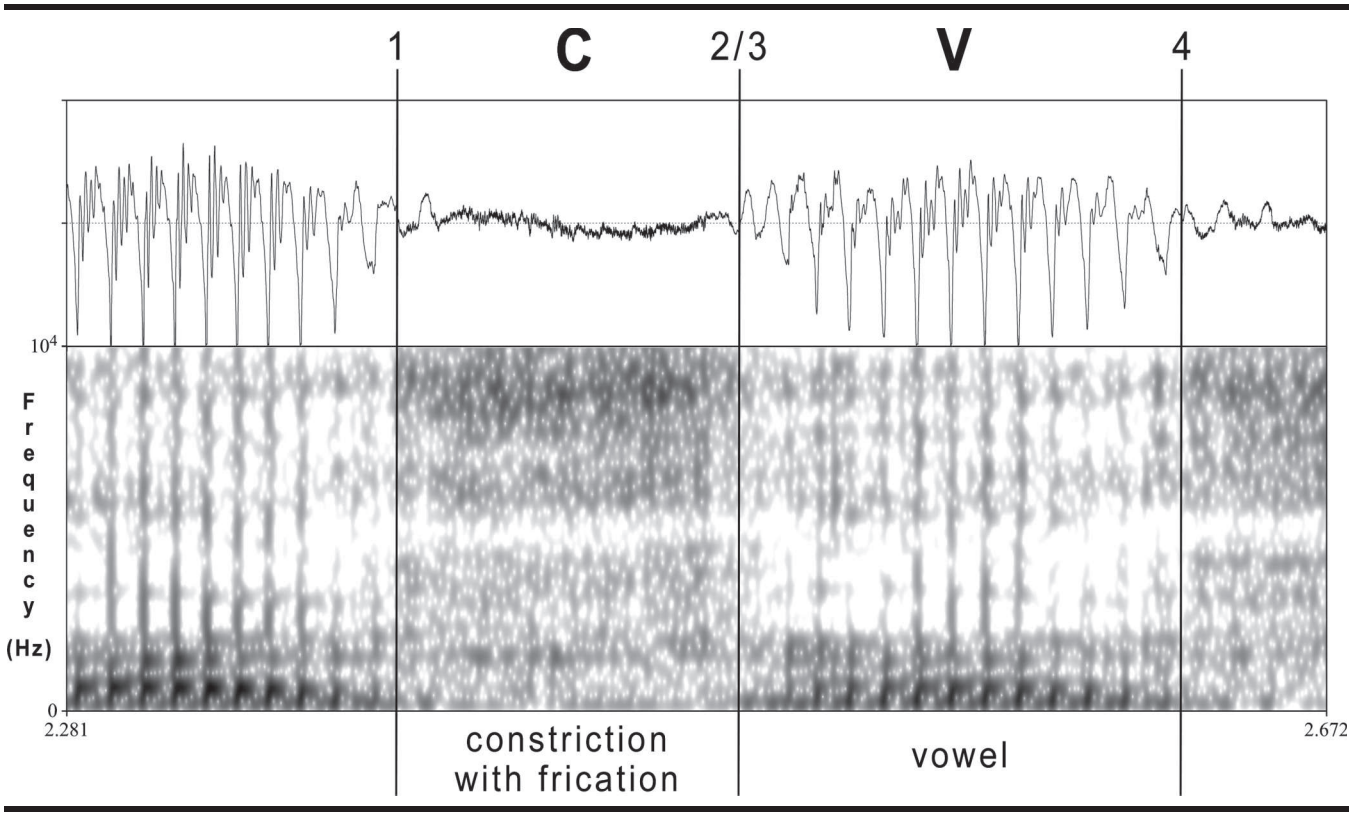


Figure 4. Labeling scheme for one syllable cycle /ka/ with frication during the consonantal constriction, taken from the essential tremor group (on-DBS). Landmarks: 1 = onset of constriction, 2/3 = offset of constriction/onset of the vowel, 4 = offset of the vowel.



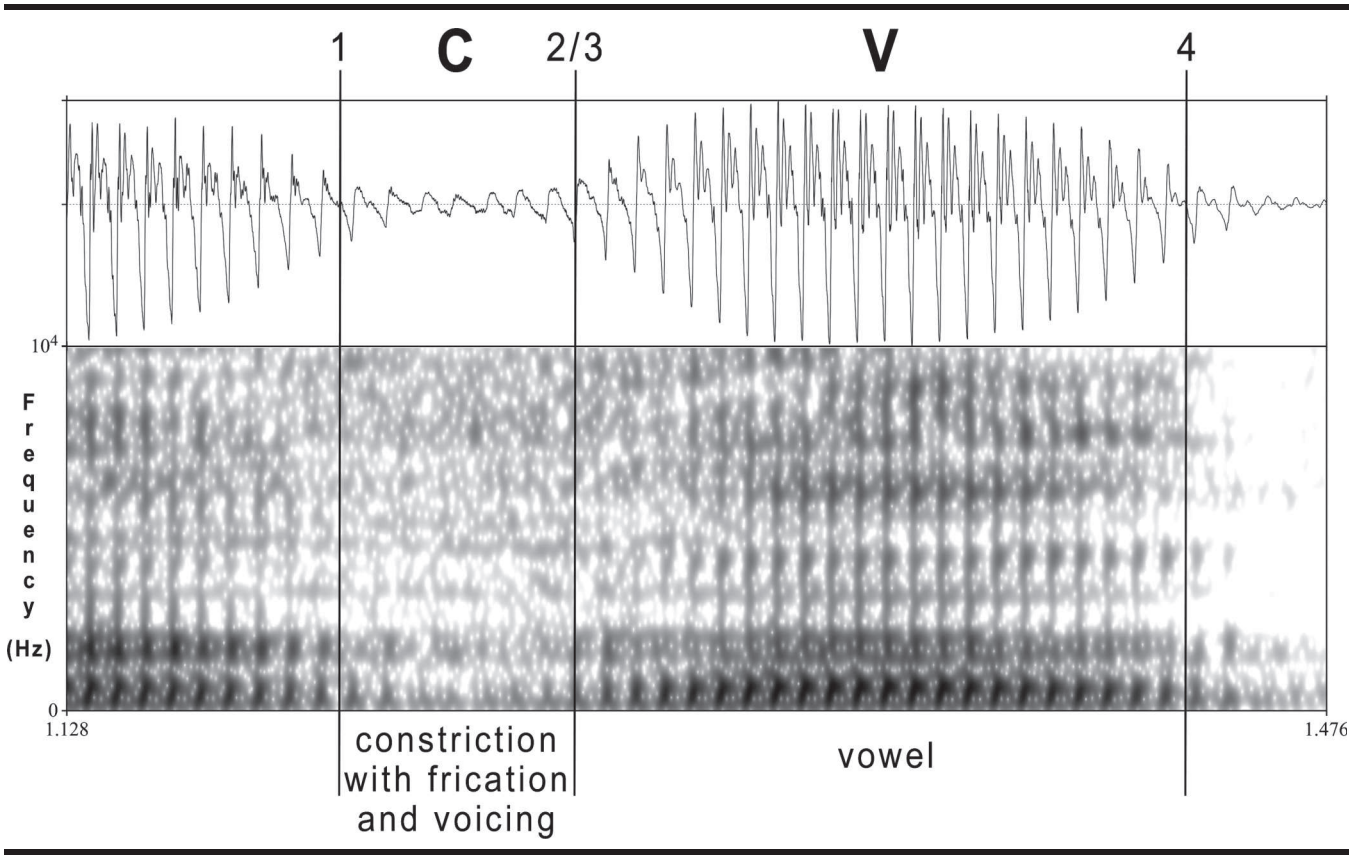
1. Syllable duration: We expect to find syllables to be prolonged as a result of slowing down the overall articulation rate (i.e. an increase in syllable duration).
2. Voicing-to-syllable ratio: We expect to find an increase of voicing perseveration during the entire syllable cycle due to insufficient glottal abduction (reduced voicing control); that is, an increase in the voicing-to-syllable ratio.
3. Voicing during constriction: We expect to find more cases of voicing during the constriction phase as a sign of poor coordination of the glottal and oral systems.
4. Frication during constriction: We expect to find more cases of frication due to imprecise oral articulation.

Statistics

All data were analyzed with generalized linear mixed models, using R (R Core Team, 2013) and the package lme4 (Bates, Maechler, & Bolker, 2012). We analyzed continuous data (i.e., syllable duration and voicing-to-syllable ratio) using Gaussian error distribution (assuming normality). For the analysis of categorical data (i.e., voicing during constriction and frication during constriction), we used a mixed logit model with a binomial error function (see Jaeger, 2008). We followed the random effect specification principles outlined by Barr, Levy, Scheepers, and Tily (2013). We included a term for random intercepts for subjects, which quantified by-subject variability. The critical fixed effect in question was DBS (coded as a categorical factor with the levels on, off, and control), for which we included random slopes for subjects (this quantifies by-subject variability in the effect of DBS stimulation). Moreover, we included place of articulation with the categorical levels /pa/, /ta/, and /ka/ and repetition as fixed effects.

In our model selection process, we tested whether one of the interactions between DBS and place of articulation or repetition, respectively, improved the model predictions significantly. This was the case for the interaction of DBS and place of articulation for both syllable duration and voicing-to-syllable ratio but never for the interaction term DBS and repetition (pointing to the fact that the observed effects were robust over repetitions). We further used subset analyses and report on the effect of DBS for each place of articulation separately. The categorical variables presence of voicing and presence of frication exhibited heavily skewed proportions of data dependent on place of articulation, which in turn, made it impossible to test for this interaction inferentially. In a second step, we validated the differences between control and off-DBS, and off-DBS and on-DBS, pairwise in subset analyses.

Figure 5. Labeling scheme for one syllable cycle /ka/ with frication in combination with voicing during the consonantal constriction, taken from the essential tremor group (on-DBS). Landmarks: 1 = onset of constriction, 2/3 = offset of constriction/onset of the vowel, 4 = offset of the vowel.



Generally, we validated the models used comparing the test model (with fixed effects) to a null model (including only the control fixed effects and the random effects) via likelihood-ratio tests. Throughout the article, we report on *p* values generated based on these likelihood-ratio tests. We used an alpha level of .05 for all statistical tests.

Results

T3 Table 3 provides an overview of all dependent measures separately for the control group and the essential tremor group in the off-DBS and on-DBS conditions. Recall that the control group is age matched to the individuals of the essential tremor group to avoid age-related effects, as found in the Weismer and Fromm (1983) and Weismer (1984) studies.

Comparing the Control Group to the Individuals of the Essential Tremor Group With Inactivated Stimulation (Off-DBS)

1. For syllable duration, there was no significant difference between control and off-DBS. For /ka/, $\chi^2(1) = 2.8$, $p = .093$; for /pa/, $\chi^2(1) = 3.15$, $p = .076$; and for /ta/, $\chi^2(1) = 2.9$, $p = .087$. Pooled over all places of articulation the control group's average syllable durations were 204 ms, compared to the off-DBS condition, which was 239 ms.
2. For the voicing-to-syllable ratio, there was no significant difference between control and off-DBS overall. For /ka/, $\chi^2(1) = 0$, $p = 1$; for /pa/, $\chi^2(1) = 0.08$, $p = .78$; and for /ta/, $\chi^2(1) = 0.69$, $p = .41$. Thus, independent of place of articulation, there was a comparable amount of voicing during the entire syllable cycle for control and off-DBS (49% and 50%, respectively).
3. For voicing during constriction, there was a significant difference between control and off-DBS, $\chi^2(1) = 5.7$, $p = .017$; so that the control group had considerably fewer instances of voicing during constriction (21.7%) than off-DBS (41.7%).
4. For the presence of frication, no significant difference was found between control and off-DBS, $\chi^2(1) = 0.7$, $p = .4$. Thus, there was a comparable amount of frication for control and off-DBS (11.7% and 16.5%, respectively).

Table 3. Means and standard deviations for all dependent variables.

Parameter	POA	Group: Control *M* (*SD*)	Control *p*	Off-DBS (and *SD*) *M* (*SD*)	Off-DBS *p*	On-DBS: *M* (*SD*)
Syllable duration (ms)	ka	223 (52.3)	*ns*	262 (76.6)	*ns*	284 (69.2)
	pa	186 (37.4)	*ns*	214 (45.8)	*ns*	218 (44.1)
	ta	201 (56.3)	*ns*	241 (59.2)	*ns*	253 (63.8)
Voicing-to-syllable ratio (%)	ka	49.9 (15.3)	*ns*	48.9 (9.7)	*	55.5 (12.2)
	pa	46.1 (16.1)	*ns*	50.3 (12.9)	*ns*	57.1 (15.5)
	ta	52.3 (13)	*ns*	50.8 (10)	*	56.8 (11.5)
Voicing during constriction (%)	ka	24.2 (43)	*	36 (48.2)	*ns*	44.7
	pa	22.5 (41.9)	*	51.9 (50.1)	*ns*	61.9
	ta	18.3 (38.9)	*	36.7 (48.4)	*ns*	51.3
Frication during constriction (%)	ka	21.7 (41.4)	*ns*	29.3 (45.7)	*	54 (50)
	pa	0	*ns*	4.4 (20.5)	*	13.1 (33.9)
	ta	13.3 (34.1)	*ns*	16.7 (37.4)	*	31.3 (46.5)

Note. POA = place of articulation. Significant differences between pairs are indicated as follows: *ns* = $p > .05$.
*$p < .05$.

Comparing the Individuals of the Essential Tremor Group in the Two Conditions, With Activated and Inactivated Stimulation

1. For syllable duration, there was no significant difference between on-DBS and off-DBS. For /ka/, $\chi^2(1) = 2.38$, $p = .12$; for /pa/, $\chi^2(1) = 1.39$, $p = .24$; and for /ta/, $\chi^2(1) = 0.31$, $p = .58$. In the on-DBS condition, average syllable durations were 252 ms compared to the off-DBS condition, which was 239 ms.
2. For the voicing-to-syllable ratio, the difference between on-DBS and off-DBS was significant for both /ka/ and /ta/: $\chi^2(1) = 10.02$, $p = .002$; and $\chi^2(1) = 4.6$, $p = .032$, respectively; but not for /pa/: $\chi^2(1) = 3.1$, $p = .079$. Under stimulation, the proportion of voicing increased by an average of 6%.
3. For voicing during constriction, there was no significant difference between off-DBS and on-DBS, $\chi^2(1) = 3.6$, $p = .059$. The number of instances exhibiting voicing during constriction increased amounts to 53% in the on-DBS condition, compared to 42% in the off-DBS condition.
4. For frication during constriction, there was a significant difference between off-DBS and on-DBS, $\chi^2(1) = 5.2$, $p = .023$, so that on-DBS had almost twice as much cases with frication (32%) than off-DBS (17%).

Discussion

Four acoustic measures were used to compare the productions of an age-matched control group and individuals of the essential tremor group with inactivated stimulation (off-DBS), and within-subject productions with activated and inactivated stimulation (on-DBS and off-DBS, respectively). For each comparison, we examine each acoustic parameter in turn.

Comparing the control group with subjects of the essential tremor group in the off-DBS condition, we found no differences in syllable duration, indicating that speakers of the essential tremor group did not have a systematically slower articulation rate. Furthermore, we found no significant difference in the voicing-to-syllable ratio, indicating that speakers with essential tremor did not produce more voicing in general. However, when comparing voicing during constriction, a difference was found. In the essential tremor group, a carryover of voicing into the voiceless consonant was found. The presence of voicing during the consonantal constriction above a threshold of 20 ms is an indicator of pathological speech (Weismer, 1984). Recall that the consonants used in this study are voiceless. Subjects with essential tremor produced voicing in the constrictions more often, indicating a more frequent delay in the opening of the glottis for voicelessness, a sign of articulation impairment, as has been reported for dysarthria in Parkinson's disease (Ackermann & Ziegler, 1989; Weismer, 1984) and multiple sclerosis (Pützer et al., 2007). Thus, perseveration of voicing into the voiceless consonant can be interpreted as a sign of dysarthria before neurogenic treatment.

For the last parameter, frication during constriction, there was a small degree of frication in both the controls and the subjects in the essential tremor group with inactivated stimulation, with no detectable significant difference across the two groups. The presence of frication during the constriction is due to a leaking oral closure, mainly involving the tongue tip against the alveolar ridge for /t/ and the tongue body against the velum for /k/. It is noteworthy that the presence of frication during the constriction is not regarded as pathological in itself. Weismer (1984) found an affinity for leaking closures of dorsal stops in the

production of young and old healthy speakers and attributed them to the sliding movement of the tongue dorsum along the soft and hard palates. However, the frequency with which it occurs has been reported to be greater in certain populations; for example, those with Parkinson's disease (Logemann & Fisher, 1981; Schweitzer, 2005; Weismer, 1984) and those with multiple sclerosis (Pützer et al., 2007).

Comparing subjects in the essential tremor group with activated and inactivated stimulation (on-DBS and off-DBS, respectively), we found no significant difference in articulation rate. This is consistent with previous studies for speakers with essential tremor (Kronenbuerger et al., 2009) and speakers with multiple sclerosis (Pützer et al., 2007). However, a different picture arises when looking at parameters at the subsyllabic (and, to some extent, subsegmental) level. Under stimulation, the voicing-to-syllable ratio increased significantly for syllables containing alveolar and velar consonants, (/tatata/ and /kakaka/) but not for labials (/papapa/). We found no effect for voicing during constriction when comparing off-DBS and on-DBS.

Moreover, we found an effect on the presence of frication during the constriction. This is in line with the results from Pützer et al. (2007) reported for VIM-DBS in individuals with multiple sclerosis. The increase of aperiodic energy during the constriction is due to incomplete oral closures under stimulation. This effect was dramatic, as frication tends to occur about twice as much under stimulation, leading to a critical deterioration in the pro- FN5 duction of stop consonants.[5]

Conclusion

In the present study, we used a set of objective acoustic measures reflecting the subjective impression of deterioration in the speech of individuals with essential tremor under stimulation. Indeed, under stimulation, we found dysarthria-like symptoms, a decrease of voiceless intervals during the entire syllable cycle accompanied by incomplete closures during the consonantal production (as evidenced by frication), while the articulation rate was stable. The decrease in voiceless intervals is due to reduced glottal control (Ackermann & Weismer, 1984; Ackermann & Ziegler, 1989; Farmer, 1980; Kent et al., 1999; Kent et al., 2000; Pützer et al., 2007; Weismer & Martin, 1992; Ziegler & von Cramon, 1987), whereas the incomplete closures are related to imprecise supralaryngeal articulation (Ackermann et al., 1995; Kent & Rosenbek, 1982; Kent et al., 1999; Logemann & Fisher, 1981; Pützer et al., 2007; Schweitzer, 2005; Weismer, 1984; Ziegler & von Cramon, 1983). Moreover, when comparing individuals of the healthy control group with those of the essential tremor group (inactivated stimulation), we found a carryover of voicing into the voiceless consonant, which can be interpreted as a sign of articulation impairment before neurogenic treatment.

Multiple reports in the literature indicate that dysarthria might occur because of the following pathophysiological mechanisms. First, stimulation current might affect motor fibers of the internal capsule located laterally to the VIM (Montgomery, 2010; Krack et al., 2002). Stimulation of the internal capsule usually presents as spastic contraction of the contralateral face or hand. In some individuals with essential tremor, face contraction and stimulation-induced dysarthria are associated. However, in other individuals with essential tremor, these two side effects occur independently. Therefore, affection of the internal capsule might not be the only explanation for stimulation-induced dysarthria.

Second, affection of the cerebellothalamic tract (see Footnote 1) per se might lead to stimulation-induced dysarthria. Not only the pathological tremor oscillations transported from the cerebellum via the VIM to the cortex but also physiological cerebellar information, which is required for coordinated speech, are transported via the cerebellothalamic tract (Ackermann, Mathiak, & Riecker, 2007) and might be affected by VIM-DBS. Therefore, stimulation-induced dysarthria could either be spastic (affection of internal capsule) or cerebellar (affection of the cerebellothalamic tract), or a combination of both.

Future studies are needed to unravel the exact pathophysiological mechanisms underlying stimulation-induced dysarthria. Furthermore, new stimulation paradigms and options are currently being developed, allowing for multiple source current steering and interleaving stimulation. It is well conceivable that these techniques will potentially alleviate stimulation induced dysarthria while maintaining the same level of tremor suppression. The assessment of success in these methods may benefit from the availability of objective quantitative measures.

[5]It is exactly this parameter that is frequently reported to be indicative of slurred speech after alcohol consumption (Künzel, Braun, & Eysholdt, 1992; Pisoni & Martin, 1989; Tanner & Tanner, 2004). It is interesting that alcohol, like DBS, reduces tremor and gait ataxia in individuals with essential tremor and induces gait disorders in healthy controls (Klebe et al., 2005; Mostile & Jankovic, 2010).

Acknowledgments AQ1

This study was supported by a grant of the German Research Foundation (DFG), Clinical Research Group 219 (KFO 219), to Lars Timmermann. We thank the participants with essential tremor for their participation in this study. We also thank Mohammad Maarouf (Department of Neurology, University Hospital Cologne), who implemented the deep brain stimulation in the individuals diagnosed with essential tremor.

References

Ackermann, H., Hertrich, I., & Hehr, T. (1995). Oral diadochokinesis in neurological dysarthrias. *Folia Phoniatrica et Logopaedica*, *47*, 15–23.

Ackermann, H., Mathiak, K., & Riecker, A. (2007). The contribution of the cerebellum to speech production and speech perception: Clinical and functional imaging data. *Cerebellum*, *6*, 202–213.

Ackermann, H., & Ziegler, W. (1989). Die Dysarthrophonie des Parkinson-Syndroms [Dysarthrophonia of Parkinson syndrome]. *Fortschritte der Neurologie und Psychiatrie*, *57*, 149–160.

Ackermann, H., & Ziegler, W. (1991). Articulatory deficits in Parkinsonian dysarthria: An acoustic analysis. *Journal of Neurology, Neurosurgery, and Psychiatry*, *54*, 1093–1098.

Barbe, M., Liebhart, L., Runge, M., Deyng, J., Florin, E., Wojtecki, L., … Timmermann, L. (2011). Deep brain stimulation of the nucleus ventralis intermedius in patients with essential tremor: Stimulation below intercommissural line is more efficient but equally effective as stimulation above. *Experimental Neurology*, *230*, 131–137.

Barr, D. J., Levy, R., Scheepers, C., & Tily, H. J. (2013). Random effects structure for confirmatory hypothesis testing: Keep it maximal. *Journal of Memory and Language*, *68*, 255–278.

Bates, D., Maechler, M., & Bolker, B. (2012). *lme4: Linear mixed-effects models using S4 classes*. Maintainer: lme4-author@R-forge.wu-wien.ac.at

Benabid, A. L., Pollak, P., Gao, D., Hoffmann, D., Limousin, P., Gay, E., … Benazzouz, A. (1996). Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. *Journal of Neurosurgery*, *84*, 203–214.

Blonsky, E. R., Logemann, J. A., Boshes, B., & Fisher, H. B. (1975). Comparison of speech and swallowing function in patients with tremor disorders and in normal geriatric patients: A cinefluorographic study. *Journal of Gerontology*, *30*, 299–303.

Boersma, P., & Weenink, E. (2010). *Praat: Doing phonetics by computer* (Version 5.1.30) [Computer program]. Retrieved from http://www.praat.org/

Carpenter, M. A., Pahwa, R., Miyawaki, K. L., Wilkinson, M. D., Searl, M. A., & Koller, W. C. (1998). Reduction in voice tremor under thalamic stimulation. *Neurology*, *50*, 796–798.

Cohen, J. (1960). A coefficient of agreement for nominal scales. *Educational and Psychological Measurement*, *20*, 37–46.

Crystal, T. H., & House, A. S. (1990). Articulation rate and the duration of syllables and stress groups in connected speech. *The Journal of the Acoustical Society of America*, *88*, 101–112.

Deuschl, G., & Elble, R. J. (2009). Essential tremor—Neurodegenerative or nondegenerative disease towards a working definition of ET. *Movement Disorders*, *24*, 2033–2041.

Devadiga, D. N., & Bhat, J. S. (2012). Oral diadokokinetic rate—An insight into speech motor control. *International Journal of Advanced Speech and Hearing Research*, *1*, 10–14.

Elble, R. J. (2013). What is essential tremor? *Current Neurology and Neuroscience Reports*, *13*, 353.

Farmer, A. (1980). Voice onset time production in cerebral palsied speakers. *Folia Phoniatrica*, *32*, 267–273.

Fleiss, J. L., & Cohen, J. (1973). The equivalence of weighted kappa and the intraclass correlation coefficient as measures of reliability. *Educational and Psychological Measurement*, *33*, 613–619.

Flora, E. D., Perera, C. L., Cameron, A. L., & Maddern, G. J. (2010). Deep brain stimulation for essential tremor: A systematic review. *Movement Disorders*, *25*, 1550–1559.

Fougeron, C., & Keating, P. A. (1997). Articulatory strengthening at edges of prosodic domains. *The Journal of the Acoustical Society of America*, *101*, 3728–3740.

Gamboa, J., Jiménez-Jiménez, F. J., Nieto, A., Cobeta, I., Vegas, A., Ortí-Pareja, M., … García-Albea, E. (1998). Acoustic voice analysis in patients with essential tremor. *Journal of Voice*, *12*, 444–452.

Gamer, M., Lemon, J., & Singh, I. F. P. (2012). *irr: Various coefficients of interrater reliability and agreement* [R package version 0.84]. Retrieved from http://CRAN.R-project.org/package=irr

Jaeger, F. T. (2008). Categorical data analysis: Away from ANOVAs (transformation or not) and towards logit mixed models. *Journal of Memory and Language*, *59*, 434–446.

Kent, R. D., Kent, J. F., & Rosenbek, J. C. (1987). Maximum performance tests of speech production. *Journal of Speech and Hearing Disorders*, *52*, 367–387.

Kent, R. D., Kent, J. F., Weismer, G., & Duffy, J. R. (2000). What dysarthrias can tell us about the neural control of speech. *Journal of Phonetics*, *28*, 273–302.

Kent, R. D., & Rosenbek, J. C. (1982). Prosodic disturbances and neurologic lesion. *Brain and Language*, *15*, 259–291.

Kent, R. D., Weismer, G., Kent, J. F., Vorperian, H., & Duffy, J. R. (1999). Acoustic studies of dysarthric speech: Methods, progress, and potential. *Journal of Communication Disorders*, *32*, 141–186.

Kingston, J., & Diehl, R. L. (1994). Phonetic knowledge. *Language*, *70*, 419–454.

Klebe, S., Stolze, H., Grensing, K., Volkmann, J., Wenzelburger, R., & Deuschl, G. (2005). Influence of alcohol on gait in patients with essential tremor. *Neurology*, *65*, 96–101.

Konstantopoulos, K., Charalambous, M., & Verhoeven, J. (2011, August 17–21). Sequential motion rates in the dysarthria of multiple sclerosis: A temporal analysis. *Proceedings of the 17th International Congress of Phonetic Sciences*, 1138–1141.

Krack, P., Dostrovsky, J., Ilinsky, I., Kultas-Ilinsky, K., Lenz, F., Lozano, A., & Vitek, J. (2002). Surgery of the motor thalamus: Problems with the present nomenclatures. *Movement Disorders*, *17*, 2–8.

Kronenbuerger, M., Konczak, J., Ziegler, W., Buderath, P., Frank, B., Coenen, V. A., … Timman, D. (2009). Balance and motor speech impairment in essential tremor. *Cerebellum*, *8*, 389–398.

Künzel, H. J., Braun, A., & Eysholdt, U. (1992). *Einfluß von Alkohol auf Sprache und Stimme*. Heidelberg, Germany: Kriminalistik Verlag. **AQ2**

Logemann, J. A., & Fisher, H. B. (1981). Vocal tract control in Parkinson's disease: Phonetic feature analysis of misarticulations. *Journal of Speech and Hearing Disorders*, *46*, 348–352.

Louis, E. D. (2009). Essential tremors: A family of neurodegenerative disorders? *Archives of Neurology*, *66*, 1202–1208.

Montgomery, E. J. (2010). *Deep brain stimulation and programming: Principles and practice*. Oxford, England: Oxford University Press.

Mostile, G., & Jankovic, J. (2010). Alcohol in essential tremor and other movement disorders. *Movement Disorders*, *25*, 2274–2284.

Nowinski, W. L., & Belov, D. (2003). The Cerefy Neuroradiology Atlas: A Talairach-Tournoux atlas-based tool for analysis of neuroimages available over the Internet. *NeuroImage*, *20*, 50–57.

Pahwa, R., Lyons, K. E., Simson, R. K., Jr., Ondo, W. G., Tarsy, D., Norregaard, T., … Jankovic, J. (2006). Long-term evaluation of deep brain stimulation of the thalamus. *Journal of Neurosurgery*, *104*, 506–512.

Pisoni, D. B., & Martin, C. S. (1989). Effects of alcohol on the acoustic-phonetic properties of speech: Perceptual and acoustic analyses. *Alcoholism: Clinical and Experimental Research*, *13*, 577–587.

Pützer, M., Barry, W. J., & Moringlane, J. R. (2007). Effect of deep brain stimulation on different speech subsystems in patients with multiple sclerosis. *Journal of Voice*, *21*, 741–753.

Putzke, J. D., Uitti, R. J., Obwegeser, A. A., Wszolek, Z. K., & Wharen, R. E. (2005). Bilateral thalamic deep brain

stimulation: Midline tremor control. *Journal of Neurology, Neurosurgery & Psychiatry*, *76*, 684–690.

R Core Team. (2013). *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing. Retrieved from http://www.R-project.org

Raethjen, J., & Deuschl, G. (2012). The oscillating central network of essential tremor. *Clinical Neurophysiology*, *123*, 61–64.

Rajput, A. H., Adler, C. H., Shill, H. A., & Rajput, A. (2012). Essential tremor is not a neurodegenerative disease. *Neurodegenerative Disease Management*, *2*, 259–268.

Raphael, L. J., Borden, G. J., & Harris, K. S. (2011). *Speech science primer: Physiology, acoustics and perception of speech* (6th ed.). Baltimore, MD: Lippincott, Williams & Wilkins.

Schnitzler, A., Munks, C., Butz, M., Timmermann, L., & Gross, J. (2009). Synchronized brain network associated with essential tremor as revealed by magnetoencephalography. *Movement Disorders*, *24*, 1629–1635.

Schweitzer, K. (2005). *Die Intonation von Entscheidungsfragen bei Morbus Parkinson unter Berücksichtigung des Sprechstils.* Unpublished master's thesis, Universität Stuttgart, Germany.

Tanner, D. C., & Tanner, M. C. (2004). *Forensic aspects of speech patterns: Voice prints, speaker profiling, lie and intoxication detection*. Tucson, AZ: Lawyers and Judges.

Victor, M., & Ropper, A. H. (2001). *Adams and Victor's principles of neurology* (*7th ed.*). McGraw-Hill.

Weismer, G. (1984). Articulatory characteristics of parkinsonian dysarthria: Segmental and phrase-level timing, spirantization, and glottal-supraglottal coordination. In M. McNeil, J. Rosenbeck, & A. Aronson (Eds.), *The dysarthrias: Physiology, acoustics, perception, management* (pp. 101–130). San Diego, CA: College Hill Press.

Weismer, G., & Fromm, D. (1983). Acoustic analysis of geriatric utterances: Segmental and nonsegmental characteristics which relate to laryngeal function. In D. M. Bless & J. H. Abbs (Eds.), *Vocal fold physiology: Contemporary research and clinical issues* (pp. 317–332). San Diego, CA: College-Hill Press.

Weismer, G., & Martin, R. E. (1992). Acoustic and perceptual approaches to the study of intelligibility. In R. D. Kent (Ed.), *Intelligibility in speech disorders: Theory, measurement and management* (pp. 67–118). Amsterdam, the Netherlands: John Benjamins.

Yang, C. C., Chung, Y. M., Chi, L. Y., Chen, H. H., & Wang, Y. T. (2011). Analysis of verbal diadochokinesis in normal speech using the diadochokinetic rate analysis program. *Journal of Dental Sciences*, *6*, 221–226.

Ziegler, W. (2002). Task-related factors in oral motor control: Speech and oral diadochokinesis in dysarthria and apraxia of speech. *Brain and Language*, *80*, 556–575.

Ziegler, W., & von Cramon, D. (1983). Vowel distortion in traumatic dysarthria. *Phonetica*, *40*, 63–78.

Ziegler, W., & von Cramon, D. (1987). Zentrale Stimmstörungen [Main voice disorders]. In L. Springer & G. Kattenbeck (Eds.), *Aktuelle Beiträge zur Dysarthrophonie und Dysprosodie* [Recent posts for dysarthrophonia and dysprosody] (pp. 59–79). Munich, Germany: Tuduv Press.

AQ3 Appendix

No.	Sex	Age	Disease duration	Months of VIM-DBS	*x* Coordinate	*y* Coordinate	*z* Coordinate	Stimulation parameters
1	M	74	64	49	L: –10	L: –5.9	L: –1.4	L: case+, 0-, 1-; 2.1 V; 60 μs; 130 Hz
					R: 12.4	R: –2.4	R: 1.3	R: case+, 0-, 1-; 2.1 V; 60 μs; 130 Hz
2	M	67	5	20	L: –10.9	L: –8.8	L: –1.5	L: case+, 0-, 1-, 2-; 1.8 V; 60 μs; 130 Hz
					R: 11.8	R: –7.1	R: –1.1	R: case+, 0-; 2.0 V; 60 μs; 130 Hz
3	M	77	19	83	L: –14.8	L: –2.9	L: 2.3	L: case+, 1-, 2-; 2.0 V; 60 μs; 130 Hz
					R: 16.6	R: –2.1	R: 3.9	R: case+, 1-; 1.5 V; 60 μs; 130 Hz
4	M	66	49	48	L: –13.1	L: –6,4	L: 4.7	L: case+, 0-, 1-; 4.3 V; 90 μs; 130 Hz
					R: 9.6	R: –5.8	R: –0.7	R: case+, 0-, 1-; 4.3 V; 90 μs; 130 Hz
5	F	73	23	61	L: na	L: na	L: na	L: case+, 0-, 1-; 1.6 V; 60 μs; 180 Hz
					R: (unilateral)	R: (unilateral)	R: (unilateral)	R: (unilateral)
6	F	73	27	30	L: –12	L: –5.1	L: 1	L: case+, 1-; 2.4 V; 60 μs; 130 Hz
					R: 12.6	R: –7.7	R: 1.3	R: case+, 1-, 2-; 2.0 V; 60 μs; 130 Hz
7	F	71	24	23	L: –11.7	L: –5.6	L: 1.4	L: case+, 1-, 2-; 3.2 V; 60 μs; 130 Hz
					R: 12.8	R: –3.1	R: 6.5	R: case+, 2-; 1.5 V; 60 μs; 130 Hz
8	M	86	10	129	L: –14.5	L: –4.9	L: 2.3	L: case+, 1-, 2-; 2.4 V; 60 μs; 130 Hz
					R: (unilateral)	R: (unilateral)	R: (unilateral)	R: (unilateral)
9	F	55	35	4	L: –10.7	L: –6.2	L: –1.2	L: case+, 0-/1-, 2-; 1.0 V/1.5 V; 60 μs; 125 Hz
					R: 10.5	R: –4	R: 1.1	R: case+, 2-; 2.0 V; 60 μs; 125 Hz
10	M	44	25	121	L: –13.8	L: –6.2	L: –2.7	L: case+, 0-, 1-; 2.3 V; 60 μs; 130 Hz
					R: 13.8	R: –5.1	R: 1.9	R: case+, 2-, 3-; 2.3 V; 60 μs; 130 Hz
11	M	74	19	50	L: –11.1	L: –7.1	L: 0.9	L: case+, 1-; 2.2 V; 60 μs; 130 Hz
					R: 11.6	R: –7.6	R: 0.9	R: case+, 1-; 2.2 V; 60 μs; 130 Hz
12	M	26	8	50	L: –9.9	L: –5.5	L: –1.2	L: case+, 0-; 3.0 V; 60 μs; 130 Hz
					R: 10.4	R: –3.8	R: –1.3	R: case+, 1-; 3.5 V; 60 μs; 130 Hz
13	M	62	29	14	L: –9.2	L: –5.7	L: –0.7	L: case+, 0-/ 1-; 2.4 V/1.0 V; 60 μs; 125 Hz
					R: 12.8	R: –2.6	R: 1.8	R: case+, 2-; 1.8 V; 60 μs; 125 Hz
14	M	70	60	29	L: –13.5	L: –7.1	L: –1.2	L: case+, 2-; 2.0 V; 60 μs; 130 Hz
					R: 10.6	R: –7.8	R: –1.1	R: case+, 1-; 1.6 V; 60 μs; 130 Hz
15	M	48	38	3	L: –11.8	L: –3.7	L: 2.1	L: case+, 1-/ 2-; 1.5 V/2.0 V; 60 μs; 125 Hz
					R: 11.3	R: –3.2	R: 1.3	R: case+, 1-; 2.0 V; 60 μs; 125 Hz
16	M	69	12	37	L: –13.1	L: –7.4	L: 1.6	L: case+, 0-, 1-/ 2-; 4.4 V/3.5 V; 90 μs; 125 Hz
					R: 10.5	R: –8.3	R: 0.7	R: case+, 0-, 1-/ 2-, 3-; 4.0 V/5.0 V; 90 μs; 125 Hz
Mean (±*SD*)		64.69 (±14.87)	27.94 (±17.57)	46.94 (±37.06)	–12.01 (±1.73) 11.95 (±1.79)	–5.9 (±1.46) –5.04 (±2.29)	0.43 (±2.02) 1.18 (±2.09)	

Note. Characteristics of subjects with essential tremor. Stereotactic coordinates from 30 electrodes implanted in the right and left VIM with reference to the midcommissural point (MCP). Stimulation parameters: amplitude (V), pulse duration (μs), and stimulation frequency (Hz). Two subjects with essential tremor were operated unilaterally. VIM = nucleus ventralis intermedius; DBS = deep brain stimulation; M = male; F = female; L = left; R = right; na = not applicable.