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Individualized current-shaping reduces DBS-induced dysarthria in patients with essential tremor

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Supplemental data at www.neurology.org

ABSTRACT

Objective: To investigate in patients with essential tremor (ET) treated with thalamic/subthalamic deep brain stimulation (DBS) whether stimulation-induced dysarthria (SID) can be diminished by individualized current-shaping with interleaving stimulation (cs-ILS) while maintaining tremor suppression (TS).

Methods: Of 26 patients screened, 10 reported SID and were invited for testing. TS was assessed by the Tremor Rating Scale and kinematic analysis of postural and action tremor. SID was assessed by phonetic and logopedic means. Additionally, patients rated their dysarthria on a visual analog scale.

Results: In 6 of the 10 patients with ET, DBS-ON (relative to DBS-OFF) led to SID while tremor was successfully reduced. When comparing individualized cs-ILS with a non–current-shaped interleaving stimulation (ILS) in these patients, there was no difference in TS while 4 of the 6 patients showed subjective improvement of speech during cs-ILS. Phonetic analysis (ILS vs cs-ILS) revealed that during cs-ILS there was a reduction of voicing during the production of voiceless stop consonants and also a trend toward an improvement in oral diadochokinetic rate, reflecting less dysarthria. Logopedic rating showed a trend toward deterioration in the diadochokinesis task when comparing ON with OFF but no difference between ILS and cs-ILS.

Conclusion: This is a proof-of-principle evaluation of current-shaping in patients with ET treated with thalamic/subthalamic DBS and experiencing SID. Data suggest a benefit on SID from individual shaping of current spread while TS is preserved.

Classification of evidence: This study provides Class IV evidence that in patients with ET treated with DBS with SID, individualized cs-ILS reduces dysarthria while maintaining tremor control.
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GLOSSARY

cs-ILS = current-shaping with interleaving stimulation; **DBS** = deep brain stimulation; **DDK** = diadochokinesis; **ET** = essential tremor; **ILS** = interleaving stimulation; **SID** = stimulation-induced dysarthria; **TRS** = Tremor Rating Scale; **TS** = tremor suppression; **TTD** = total travel distance; **VAS** = visual analog scale.

Thalamic/subthalamic deep brain stimulation (DBS) is effective in essential tremor (ET), reducing tremor by 60% to 80%.[1] However, stimulation-induced dysarthria (SID) is a common side effect, affecting approximately 10% of patients.[1] In a phonetic study with 15 patients with ET, we observed an increase of voicing when ventral intermediate nucleus–DBS was activated, reflecting slurred speech.[2] To date, it remains controversial whether stimulation of the target area itself or current spread affecting neighboring structures causes SID.[3] SID and other side effects occur more often during activation of ventral contacts, especially when high current is used.[3] This leads to the dilemma of choosing suboptimal stimulation parameters (i.e., amplitudes below the SID threshold) to avoid dysarthria at the cost of reduced tremor suppression (TS). Interleaving stimulation (ILS) describes the possibility of running different stimulation

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programs on the same DBS electrode in a temporally alternating sequence. So far, the neurobiological consequences of ILS are unknown. This new method also allows for individual current-shaping because different current amplitudes can be administered on different contacts, which might help to achieve greater efficacy and fewer side effects.[3] Theoretically, individualized current-shaping by amplitude reduction below the SID threshold, together with activation of a second, more dorsally located contact with higher stimulation amplitude, might reduce dysarthria while preserving TS. Three case reports and one case series (n = 4) suggest better outcomes of DBS during current-shaped ILS (cs-ILS).[4–7] In a recent study, cs-ILS was used for combined nigral and subthalamic stimulation, which resulted in an improvement of freezing of gait in patients with Parkinson disease compared with subthalamic DBS alone.[8] While these studies used cs-ILS for better DBS outcome, they did not systematically investigate the effect of current-shaping. Therefore, there is currently no proof-of-principle evaluation of current-shaping in ILS. This systematic, double-blind, exploratory study compared a regular ILS condition (2 active contacts with the same current amplitudes) with a current-shaped condition (cs-ILS, current shifted to the dorsal contact) regarding TS and SID. The intention of the present study was not to show superiority of a stimulation concept (i.e., ILS) but of the concept of current-shaping for reduction of SID.

METHODS **Standard protocol approvals, ethics, and patient consents.** The study was approved by the local ethics committee. Patients gave written informed consent before study participation.

Primary research questions. We hypothesized that current-shaping reduces dysarthria (superiority: voicing and visual analog scale [VAS] reduction) without losing the effect on TS (noninferiority: Tremor Rating Scale [TRS] and kinematic analysis of postural tremor). The evidence for both research questions is classified as Class IV because of the absence of a comparison group.

Patients. We screened 26 patients with ET who had received a DBS system capable of ILS (ACTIVA RC/PC; Medtronic Inc., Minneapolis, MN). Ten of these patients reported a deterioration of speech postoperatively and 6 (23%) reported an improvement of speech (at least 10 points on the VAS) when the DBS device was turned off and were thus included in the study (table; electrode localization in figure e-1 on the *Neurology*® Web site at www.neurology.org).

Tremor analysis. Tremor was measured using a movement analysis system (CMS 20; Zebris Medical GmbH, Isny,

Table Patient characteristics and stimulation parameters

Patient	Age, y	Sex	Disease duration, y	Duration of DBS, mo	Electrode responsible for dysarthria	Contacts used in ON	Amplitudes used in ON,[a] mA	Contacts used in ILS/cs-ILS	Amplitudes used in ILS, mA	Amplitudes used in cs-ILS, mA	Contralateral settings, amplitudes in mA	
1	71	M	33	36	R	10−	1.4	9−/10−	1/1	0.5/1.5	0−/1−	1.4/1.4
2	72	M	7	22	L	9−/10−	0.6/0.8	9−/10−	1.5/1.5	1.0/2.0	1−/2−	0.5/1.0
3	65	M	32	42	L	0−/1−	1.7/0.7	0−/1−	2/2	0.5/3.5	9−/10−	1.2/2.7
4	58	F	14	132	L	0−/1−/2−	0.7/1.9/1.9	1−/2−	3/3	2/4	10−	2.2
5	72	M	9	39	L	0−	1.3	1−/2−	1/1	0.5/1.5	8−	3.5
6	78	F	11	41	R	8−/9−/10−	3.6/3.6/3.2	8−/9−	3.5/3.5	2/5	2−	3.2

Abbreviations: cs-ILS = current-shaped interleaving stimulation; DBS = deep brain stimulation; ILS = interleaving stimulation.
Characteristics and stimulation parameters of patients included in the study. In all stimulation conditions, the casing had a positive polarity (C+).
[a] When original settings used voltage-controlled stimulation, we calculated the respective currents for better comparability. Note that the dysarthria-inducing electrodes of patients 1 and 5 with relatively low amplitude were located more laterally compared with the mean x coordinate ($x_{mean} = 11 \pm 1.24$ mm; $x_{patient\ 1} = 12.9$ mm; $x_{patient\ 5} = 11.8$ mm).

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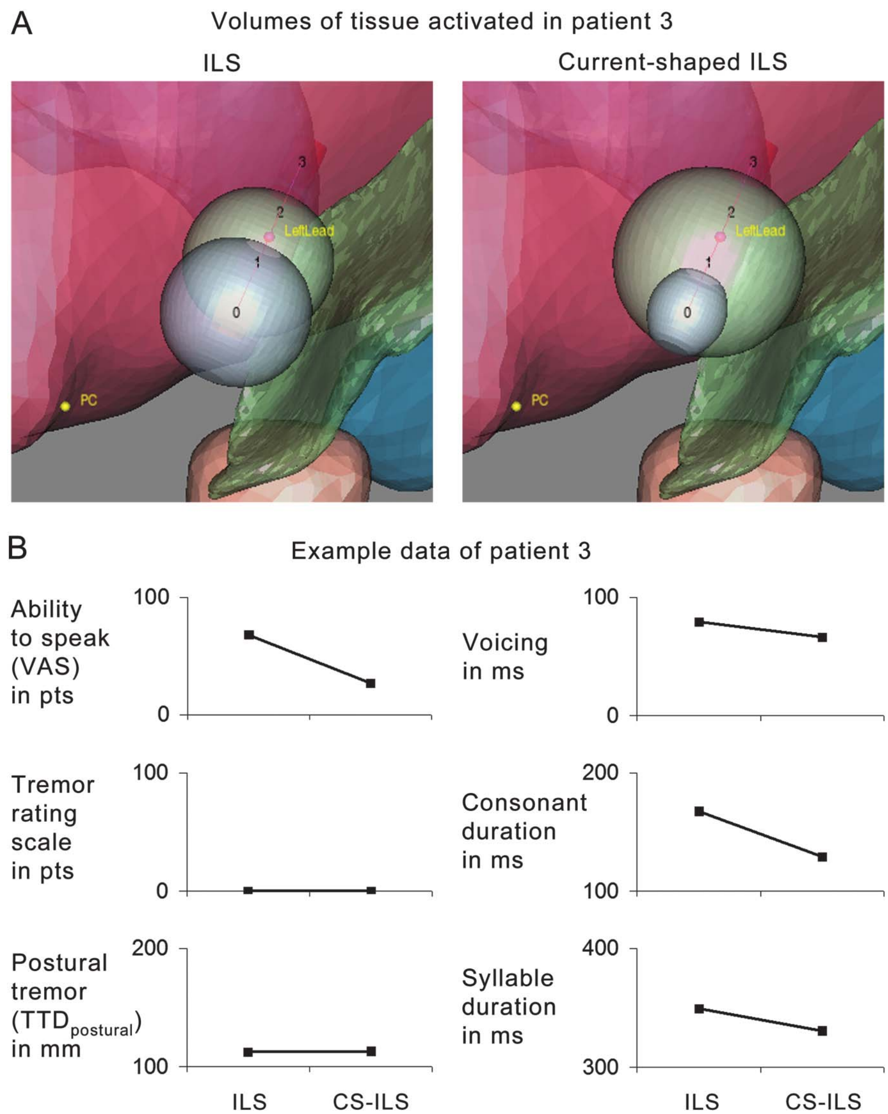
Germany). Patients performed a postural and a reach-grip task. The average total travel distance (TTD) was used for quantification of postural ($TTD_{postural}$) and action (TTD_{action}) tremor as described previously.[9] In addition, patients were videotaped performing motor parts of the TRS.[10] Videos were rated by J.R., who was blinded for the stimulation condition.

Analysis of dysarthria. Speech was digitally recorded in a sound-attenuated booth for the following tasks: maximum phonation time, oral diadochokinesis (DDK), spontaneous speech, and a read text. Patients rated their "ability to speak" on a VAS (from 0 [normal] to 100 mm [worst]). Recordings were assessed independently and blinded by 2 linguists. Logopedic rating was evaluated with the Frenchay Dysarthria Score. Phonetic analysis was based on the DDK task as used previously,[2] and the following parameters were measured: syllable, consonant, vowel, and closure duration; voice-onset time; friction and voicing during closure; and phonation.

DBS programming algorithm. Patients were tested with stimulation ON and OFF. The electrode inducing SID (determined by switching off the electrodes separately) was tested on all contacts for TS from 0 to maximum 5 mA in 0.5-mA intervals. For ILS, the most effective contact was used plus the one dorsal to it. By increasing the amplitudes in 0.5-mA intervals and using an instantaneous MATLAB-based (The MathWorks Inc., Natick, MA) analysis, we determined the best TS (lowest $TTD_{postural}$). The best cs-ILS was determined by shifting current

Figure 1 **Electrode localization of one patient with exemplary tremor and speech parameters**



(A) Electrode localization and simulation of the volume of tissue activated was performed with Optivise (Medtronic Inc.) for the left electrode of patient 3 during interleaving stimulation (ILS) and current-shaping ILS (cs-ILS) conditions. Individual anatomical landmarks: the thalamus is shown in magenta, the ventral intermediate nucleus inside the thalamus in dark blue, the red nucleus in orange, the zona incerta in green, and the subthalamic nucleus in light blue. Note that with ILS, the 2 pulses are not applied simultaneously to the tissue (as implicated here) but in a temporally alternating sequence. (B) In this patient, when comparing cs-ILS with ILS, there was an improvement of speech parameters, especially self-reported overall speech on the visual analog scale (VAS) (in pts [points]), with no deterioration of tremor control measured with the Tremor Rating Scale (TRS) and kinematic analysis of postural tremor ($TTD_{postural}$ = total travel distance of postural tremor).

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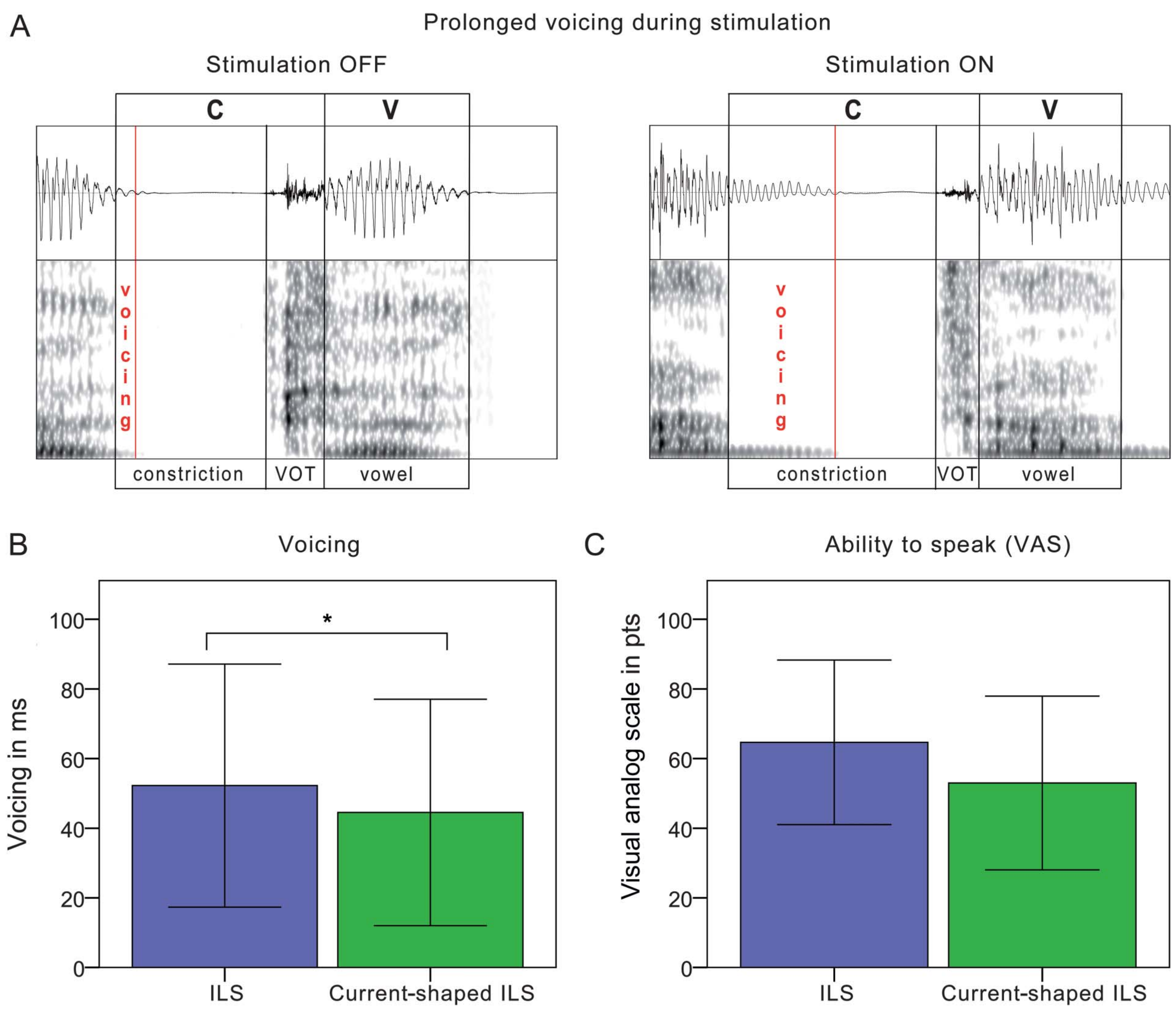
from the ventral to the dorsal contact in 0.5-mA steps as long as there was no recurrence of tremor (defined as a 10% increase of the $TTD_{postural}$ compared with ILS). We waited at least 5 minutes between changes of stimulation parameters. The final stimulation conditions were applied for at least 30 minutes. Stimulation was performed at frequencies of 125 Hz and pulse widths of 60 μs. During the ILS/cs-ILS condition, the electrode not responsible for SID was left in its original settings. Randomization was impossible because of this predefined programming algorithm.

Statistics. According to our hypotheses, we used 1-sided tests (paired *t* test/Wilcoxon signed-rank test) for the ON/OFF comparison. For the ILS/cs-ILS comparison, we used 1-sided tests for speech parameters and 2-sided tests for tremor parameters. According to the exploratory character of this study, data were not α-corrected for multiple parameters.

RESULTS Electrode location and parameters of an example patient are shown in figure 1. Overall, patients had significantly less tremor in the ON condition than in the OFF condition (TRS $p = 0.047$, $TTD_{postural}$ $p = 0.03$, TTD_{action} $p = 0.046$) and a subjective deterioration of speech in stimulation ON (VAS $p = 0.031$). In line with our previous study,[2] the oral DDK rate also deteriorated as shown by the phonetic parameters of syllable duration ($p = 0.021$), vowel duration ($p = 0.026$), and consonant duration ($p = 0.02$). Logopedic evaluation showed a trend toward deterioration of speech in the DDK task during DBS ON ($p = 0.063$). As expected, when comparing ILS and cs-ILS, patients did not show a difference in TS (TRS $p = 0.50$, $TTD_{postural}$ $p = 0.438$, TTD_{action} $p = 1.0$) but a trend toward subjective improvement of speech during cs-ILS (4 of 6 patients improved according to the VAS,

Figure 2 Speech parameters in ILS and cs-ILS



(A) Acoustic waveform and spectrogram of one syllable /ka/ during oral diadochokinesis, showing prolonged voicing (marked red) during the stop consonant's constriction phase in the stimulation ON condition (C = consonant; V = vowel; VOT = voice onset time). (B) Comparison of voicing during the production of voiceless stop consonants in interleaving stimulation (ILS) and current-shaping ILS (cs-ILS). Voicing is reduced during cs-ILS ($p = 0.047$), reflecting less dysarthria. (C) Comparison of self-reported overall speech (visual analog scale [VAS] in points [pts]) in ILS and cs-ILS. There is a trend for overall speech improvement during cs-ILS ($p = 0.094$). All diagrams show arithmetic means (±1 SD). The asterisk marks a significant difference ($p < 0.05$).

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$p = 0.094$; figure 2). Consistently, phonetic analysis revealed a reduction of voicing during the production of voiceless stop consonants ($p = 0.047$, figure 2) and also a trend toward an improvement of oral DDK rate (syllable duration $p = 0.056$, consonant duration $p = 0.08$) during cs-ILS, thus reflecting reduced SID. Logopedic rating showed no difference between ILS and cs-ILS.

DISCUSSION This is a proof-of-principle study investigating current-shaping for reduction of SID. This exploratory study was controlled for various aspects: first, we controlled for potential neurobiological effects of ILS per se because both parameter settings were programmed in an interleaved fashion; second, we used the same total amount of current and the same contacts in both conditions, allowing us to conclude that observed changes are solely attributable to current-shaping. Furthermore, not only were tremor and speech parameters analyzed in a blinded manner, but patients were also unaware of the stimulation mode. Because ILS and cs-ILS suppressed tremor equally well, they were indistinguishable by the patients. Furthermore, we stimulated with constant current rather than voltage-dependent in order to compensate unequal impedances of different electrode contacts. Any inferences that can be drawn from this study need to be considered in light of the small number of patients included. However, one has to bear in mind that only 10% of patients develop SID and until now there was only a small population of patients who had been provided with an ILS-capable device. In summary, the data suggest that current-shaping, in principle, reduces side effects while maintaining the beneficial effects of DBS.

AUTHOR CONTRIBUTIONS

Dr. Barbe: study concept and design, acquisition of data, analysis and interpretation, first draft of the manuscript. Mr. Dembek: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content. Mr. Becker: analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. Raethjen and Dr. Hartinger: analysis of data, critical revision of the manuscript for important intellectual content. Dr. Meister: critical revision of the manuscript for important intellectual content. Dr. Runge: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Maarouf and Dr. Fink: critical revision of the manuscript for important intellectual content. Dr. Timmermann: study concept and design, critical revision of the manuscript for important intellectual content, study supervision.

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