Supporting Data

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Directional Deep Brain Stimulation of the Subthalamic Nucleus: A Pilot Study Using a Novel Neurostimulation Device

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ABSTRACT

Introduction: A novel neurostimulation system allows steering current in horizontal directions by combining segmented leads and multiple independent current control. The aim of this study was to evaluate directional DBS effects on parkinsonian motor features and adverse effects of subthalamic neurostimulation.

Methods: Seven PD patients implanted with the novel directional DBS system for bilateral subthalamic DBS underwent an extended monopolar review session during the first postoperative week, in which current thresholds were determined for rigidity control and stimulation-induced adverse effects using either directional or ring-mode settings.

Results: Effect or adverse effect thresholds were modified by directional settings for each of the 14 STN leads. Magnitude of change varied markedly between leads, as did orientation of optimal horizontal current steering. Conclusion: Directional current steering through chronically implanted segmented electrodes is feasible, alters adverse effect and efficacy thresholds in a highly individual manner, and expands the therapeutic window in a monopolar view as compared to ring-mode DBS. © 2016 The Authors. Movement Disorders published by Wiley Periodicals, Inc. on behalf of International Parkinson and Movement Disorder Society

Key Words: deep brain stimulation; Parkinson's disease

DBS of the STN has proven to be a safe, effective treatment for patients with severe tremor, motor fluctuations, or dyskinesia in Parkinson’s disease. However, individual outcomes may vary greatly and critically depend on the brain volume being stimulated. Best motor symptom control has been associated with stimulation of the dorsolateral STN, whereas current leaking into adjacent fiber tracts can cause adverse effects such as dysarthria, impaired fine motor control, or oculomotor disturbances.

Conventional DBS systems use ring-shaped electrodes, which generate an approximately spherical electrical field. In these systems, programming of polarity and stimulation pulse parameters allows only limited control of the shape of the volume of tissue activated. Recently, two acute intraoperative studies have proven the feasibility of horizontal current steering by using novel lead designs, such as segmented or multicontact electrodes. Directed stimulation using these electrodes resulted in increased stimulation thresholds for side effects as compared to standard spherical stimulation.

Here, we report our first clinical experience of directional DBS with a novel, fully implantable neurostimulation system (Vercise PC; Boston Scientific, Valencia, CA), which combines eight-contact directional leads and a pulse generator capable of multiple independent current source control (MICC). The system received a CE Mark in September 2015, and the first device was implanted at our center on 16 September 2015.

The novel directional DBS lead has four electrode levels, of which the two middle levels are split into three segments spanning approximately 120 degrees, whereas the highest and lowest level consist of ring-shaped electrodes (Supporting Fig. 1A). MICC allows to distribute the stimulation current over any combination of electrodes of one lead in arbitrary proportions. An equal distribution of current among all three segments at one level simulates a ring-shaped electrode, whereas maximal horizontal steering effects are obtained when current is distributed to one or two segments at one level (Supporting Fig. 1B). Our retrospective analysis of monopolar review data aimed at quantifying the effect of horizontal current steering on the therapeutic window of STN-DBS as compared to conventional ring mode stimulation.

Patients and Methods

Seven PD patients (2 female; age, 47–64 years; disease duration: 8–20 years; UPDRS-III Med off: 42; UPDRS-
ed electrical fields with a field vector rotated by either

patients). This programming results in up to six direct-

between two adjacent segments (subsequent 6

additionally evaluating equal current distributions
each level were tested by either restricting cathodal

ring level." Then, different stimulation directions at

levels of each lead in ring mode (equally distributing
current among the three segments of a level) and

hypotonia of the upper extremity) was achieved or an

steps of 0.5 mA until complete rigidity suppression (i.e.,

able pulse generator case was always programmed as

system in the practica lly defined medication

went an extended programming session of their DBS

on III Med on 19), who had been implanted with the direc-
tional Vercise PC (Boston Scientific) for bilateral STN-

DBS between September and December 2015, under-
went an extended programming session of their DBS

in the practically defined medication off state
(>12 hours of medication withdrawal) 4 to 9 days (mean,
7 ± 2) postsurgery. The programming session was sched-
uled when the stun effect of electrode placement was
decreasing and testable off period motor symptoms had

returned in each patient in at least one body side.

The programming session followed the procedure of a
standard monopolar review,5 in which for each electrode
configuration current thresholds are determined for com-
plete rigidity control (efficacy threshold) and the first
adverse event (AE) limiting further current increase (AE
threshold). Frequency and pulse width were constantly
set to 130 Hz and 60 μs, respectively, and the implant-
able pulse generator case was always programmed as
anode. Stimulation current was increased/decreased in
steps of 0.5 mA until complete rigidity suppression (i.e.,
hypotonia of the upper extremity) was achieved or an
AE of stimulation was reported by the patient or
observed on clinical examination. Then, the current
threshold was fine tuned in smaller steps of 0.1 mA.

Using this procedure, we first determined the ther-
apeutic window (TW; current difference between effica-
cy and AE threshold in mA) for the two segmented
levels of each lead in ring mode (equally distributing
current among the three segments of a level) and
labeled the level with the larger TW as "most effective
ring level." Then, different stimulation directions at
each level were tested by either restricting cathodal
current to each of the three segments (first patient) or
additionally evaluating equal current distributions
between two adjacent segments (subsequent 6
patients). This programming results in up to six direct-
ed electrical fields with a field vector rotated by either
120 or 60 degrees (Supporting Figs. 1B and 2). The
sequence of levels or horizontal directions tested was
left to the programming physician's discretion, who
was unaware of the anatomical position and orienta-
tion of the lead within STN. Threshold amplitudes
were compiled in a datasheet and later used for con-
structing individual polar plots (see Supporting Fig. 2)
and descriptive statistics (paired two-sample t test).

Results

We could determine efficacy thresholds for only 11 of
14 STNs, because a persistent microlesioning effect pre-
vented reliable rigidity assessment in the others, whereas
AE thresholds were determined for all 14 STNs. The AEs
determining the upper limit of the TW were contractions
of facial or hand muscles in 11 of 14 STNs, dysarthria in
6 of 14, and persisting dysesthesia in 1 of 14.

In total, we assessed 154 directional and 28 ring-
mode settings and determined TW for 111 and 24 set-
tings, respectively. For each directional setting, the
proportional change of TW from corresponding ring-
mode stimulation was calculated, with negative values
indicating a reduction and positive values indicating
an increase of the TW. The proportional change was
highly variable between leads and directional settings
and ranged between −100% and 440% (see Table 1).
Interestingly, this change in TW was not only deter-
mined by a variable AE threshold, but also by vari-
ations in the effect threshold (see Supporting Fig. 3).

By fusing the postoperative cranial CT with the pre-
operative MRI (Leksell Surgiplan; Elekta Instrument
AB, Stockholm, Sweden) and identifying the directional
lead marker, we determined the orientation of each lead
within stereotactic space and assigned each directional
setting to an orientation in relation to the anterior com-
mis sure/posterior commissure (AC-PC) line (e.g., anteri-
or, anterolateral, etc.). This allowed us to identify the
anatomical direction of the current vector providing the

| ID | Side | At level | Best direction | Best ΔTW (%) | Worst direction | Worst ΔTW (%) | Best direction | Worst direction | ΔTW (%) |
|----|------|----------|---------------|--------------|----------------|--------------|---------------|----------------|---------|
| 01 | Left | 5-6-7    | post-med      | 35           | post-lat       | 42           | post-med      | 2-3-4          | 57       |
| 01 | Right| 13-14-15| ant           | 9            | post-lat       | −9           | post-med      | 10-11-12       | 9        |
| 02 | Left | 5-6-7    | post-med      | 28           | post-lat       | 48           | post-med      | 2-3-4          | 57       |
| 02 | Right| 10-11-12| ant           | 10           | post-lat       | −50          | post-med      | 13-14-15       | 100      |
| 03 | Right| 10-11-12| ant-lat       | −6           | ant-lat        | −65          | post-med      | 13-14-15       | −3       |
| 04 | Right| 10-11-12| post-med      | 27           | ant-lat        | −44          | post-med      | 13-14-15       | 77       |
| 05 | Left | 2-3-4    | med           | 88           | post-med       | 0            | post-med      | 5-6-7          | 171      |
| 05 | Right| 13-14-15| post           | −5           | post-lat       | −52          | ant-med       | 10-11-12       | 135      |
| 06 | Right| 13-14-15| lat           | −9           | lat            | −75          | post-med      | 10-11-12       | 47       |
| 07 | Left | 2-3-4    | ant-med       | −8           | ant-med        | −72          | post-med      | 5-6-7          | 135      |
| 07 | Right| 13-14-15| post           | 9            | post           | −18          | post-med      | 10-11-12       | 50       |

Changes in therapeutic window (ΔTW) in best and worst direction and respective orientation of electrical field vector are given for all STN in which effect and AE threshold could be determined.

post-med, postero medial; ant, anterior; ant-med, anteromedial; med, medial; post, posterior; lat, lateral; post-lat, posterolateral; ant-lat, anterolateral.
highest positive change in TW (best orientation) and the smallest change (worst orientation) for each lead and level. As expected from variable lead locations within a variably shaped and oriented STN, there was no uniform best direction, and best versus worst orientation were often, but not always strictly opposite (see Table 1). Most often, the “optimal” field vector was oriented in an “anterior” or “posteromedial” direction.

After grouping the results of directional stimulation by ring level, it became apparent that larger TW effects of optimal current steering could be observed at the less effective (111 ± 122%; median, 77; range, –3 to 440) as compared to the most effective level (16 ± 22%; median, 9; range, –9 to 88%; see Fig. 1). The notion of a larger TW with directional DBS is also supported by a secondary analysis comparing the amplitude range between efficacy and AE threshold of optimal current steering at the most effective level compared to ring mode (4.0 ± 1.5 vs. 3.6 ± 1.4 mA; *P* = 0.06).

Interestingly, the change in TW was driven only by an increase in AE threshold at the most effective level, whereas at the less effective level, both efficacy and AE thresholds, changed significantly in favor of the optimal direction (1.25 ± 1.23 vs. 1.77 ± 0.95 mA; *P* = 0.05; 5.39 vs. 4.27 ± 1.46 mA; *P* < 0.005).

At the end of the monopolar review, the optimal directional settings were programmed in all patients and gradually adjusted according to clinical needs during the subsequent days of hospitalization. After a follow-up of 3 to 6 months (median, 4), all patients have remained programmed in directional mode without need of rescue programming into ring mode to improve stimulation efficacy (see Supporting Table 1). None of the patients are complaining about stimulation induced adverse effects so far.

**Discussion**

Our results demonstrate, for the first time, the feasibility of horizontal current steering using a fully implanted neurostimulation device with directional leads and MICC technology. Despite the limitations of an acute monopolar review in the early postoperative period, they also provide first evidence of a beneficial impact of directional DBS on the TW. In theory, a larger TW would offer more programming flexibility for optimizing the efficacy of DBS and reduce the likelihood of inadvertently exceeding the adverse effect threshold, when the stimulation amplitude is gradually adjusted during the subsequent stabilization period.6 Hence, directional DBS should result in more consistent good outcomes and lower AE rates across groups of patients, whereas it is unlikely to provide more benefit than an optimally implanted ring-mode DBS in an individual.

Not unexpectedly, we found a larger effect of directional DBS at the less beneficial lead level. This indicates that the individual clinical benefit of directional DBS is best observed for suboptimal electrode positions resulting in a narrow TW, for example, if the electrode is placed too laterally within the STN close to the internal capsule. Hence, directional DBS may be able to compensate within certain limits for small deviations of the lead from the optimal functional target, which are a main source of outcome variability in STN-DBS even in experienced surgical centers.4 However, as a note of caution, the availability of a directional DBS system must never be an excuse for lowering the surgical standard and precision of surgical lead placement. In fact, the implantation of the Vercise directional lead is surgically more challenging, because the active site has a reduced span, compared to the standard eight-contact ring lead, and the split contacts need to be exactly aligned in depth with the dorsolateral motor region of the STN. Moreover, lead rotation is introduced as an additional degree of freedom during the implantation and needs to be controlled for by exact alignment of the rotational lead marker with patient centric landmarks (e.g., AC-PC line).

Other limitations of our study include the unblinded and subjective clinical rating of rigidity and adverse effect thresholds, lack of long-term clinical follow-up, early postoperative time period with a partially persistent stun effect, and small number of subjects. Importantly, we report feasibility data obtained during an
acute stimulation challenge, but no efficacy data on the
use of chronic directional DBS compared to standard
ring DBS. Nevertheless, our findings may provide valu-
able input into the planning of appropriate
clinical trials, which are now needed to establish the
theoretical advantages of directional DBS in clinical
practice and on a group level, but should also take into
account possible disadvantages of the expanded parame-
ter space, such as increased programming burden.

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Appendectomy in Mid and Later Life and Risk of Parkinson's Disease: A Population-Based Study
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ABSTRACT
Introduction: Pathogenic movement of alpha-synuclein from the gut to the brain in PD has been proposed. The appendix has a relatively high density of alpha-synuclein deposition in neurologically healthy individuals. It has been proposed that the initiating events of Parkinson's disease (PD) may occur outside the central nervous system (CNS), with secondary spread to the brain through a prion-like process. The gastrointestinal tract is a candidate for a location of initiating events. In people without PD, Gray and colleagues found that alpha-synuclein immunoreactivity was most abundant in the appendiceal lamina propria compared to the gastric mucosa or other parts of the right colon, colocalized with neural markers, and was close to the luminal surface of the appendix, putting it in close proximity to any pathogen or triggering event within the gut. The lack of a blood-tissue barrier in the appendiceal mucosa would facilitate contact between a blood-borne agent and the enteric nervous system and exogenous agents contacting the host.

Methods: Using cause-specific hazards regression models, we compared persons over 35 years of age who had undergone appendectomy with two groups of age- and sex-matched individuals having had: (1) a cholecystectomy and (2) neither procedure. Subse-
quent diagnoses of PD were identified.

Results: Among 42,999 individuals undergoing appendec-
tomy, no difference in risk of PD was identified compared to
cholecystectomy (hazard ratio = 1.004; 95% confidence
interval: 0.740–1.364). Compared with no procedure, indi-
viduals with appendectomy had a higher incidence of PD
within 5 years, but no significant difference in risk thereafter.

Conclusion: In our study, appendectomy in mid or late
life does not appear to be associated with a reduced
risk of PD. © 2016 International Parkinson and Move-
ment Disorder Society

Key Words: Parkinson's disease; appendectomy; etiology

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