Research/trial program:

The Swedish Essential Tremor (SWEET) Trial – A Multicentre Randomized Controlled Trial of Deep Brain Stimulation for Essential Tremor

2018-12-20

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PURPOSE AND AIMS

- Aim 1 - To evaluate the effect of deep brain stimulation (DBS) vs best medical treatment in essential tremor (ET) in a randomized, single-blinded controlled trial.
- Aim 2 - To compare the effect of DBS in the established target in the ventrolateral (VL)-thalamus/ nucleus ventralis intermedius thalami (Vim) and in a new target in the posterior subthalamic area (PSA)/caudal Zona incerta (cZi).
- Aim 3 - To map the target area in the VL-thalamus and PSA concerning effects and side effects of stimulation in order to identify and delineate the optimal target.
- Aim 4 - To evaluate the long-term effects of DBS for ET in a longitudinal non-randomized evaluation.

SURVEY OF THE FIELD

Deep Brain Stimulation (DBS)

In DBS, thin quadripolar electrode leads (with four 1.5 mm long and 1.27 mm thick contacts, separated by 1.5 mm space), connected to a neuropacemaker are implanted with stereotactic technique into the central parts of the brain (Figure 1) where the neuronal activity is modulated with electrical current. DBS has revolutionised the treatment of Parkinson´s disease and other movement disorders, and more than 150.000 patients have so far been operated[29]. Currently, new indications and targets are emerging[21].

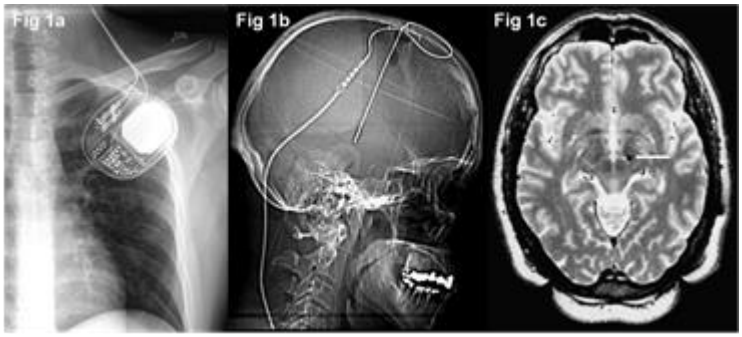


Figure 1. Implanted DBS system

However, many of the brain targets subjected for DBS are not well defined, and one of the main problem with DBS is likely to be the high number of suboptimally placed electrodes with lack of effect, unacceptable side effects and costly revisions[10, 31]. Further, even though this is an invasive and highly resource demanding therapy, most clinical indications for DBS (asides from Parkinson´s disease and dystonia) are not evidence based[8, 12, 13]. They are considered as "established treatments" and often provided as clinical treatment and not within the context of trials or scientific studies.

DBS for Essential Tremor

ET is the most common adult movement disorder with a prevalence of about 5% in the population above 65 years of age. Of patients who seek medical care up to 50% do not respond adequately to drug therapy[27].

The thalamic nucleus ventralis intermedius (Vim) is the projection structure of the cerebello-thalamic fibres mediating tremor. Hence, Vim has been an "established" target for surgical treatment of ET during the thalamotomy era, and when DBS was introduced and replaced thalamotomy, the Vim was logically the target for DBS for tremor. However, data from recent years indicate that it might not be stimulation of the Vim itself, but rather, the stimulation was affecting the pathologic tremor oscillations mediated by the cerebello-

thalamic-cortical projections, located in the PSA and the caudal zona incerta (cZi)[3, 17, 24]. Thus, a number of studies have demonstrated that electrode contacts that reach the PSA have a better effect on tremor than those located more dorsally-rostrally in the Vim. This subthalamic area, which is situated immediately ventral-caudal to the Vim, is particulary dense with cerebello-thalamic axons, dispersing into the Vim. Stimulation is thus likely to involve more axons in the PSA than in the Vim, since these axons in the PSA constitute so to speak a bottle neck of the axonal traffic mediating tremor. It is also plausible that stimulation of axons rather than stimulation of nuclei actually affects by antedromic and orthodromic propagation more neurons and therefore also alters tremor oscillations more efficiently [24]. A number of studies directly targeting the cZi have also recently presented results comparing favorably with the results published for Vim DBS[3, 6, 17, 19, 34].

Level of evidence regarding DBS in ET:

Neither the Vim nor the cZi are evidence based targets, and there are no evidence-based DBS procedures for ET (level IV evidence only)[8, 12], even though this is the second most common indication for DBS. However, the Vim is by tradition the established target for ET and the procedure is recommended in the Swedish guidelines for treatment of tremor[37].

The results of Vim DBS ET have been demonstrated in a number of uncontrolled, mostly minor studies[1, 12]. A problem is that many of these studies are likely to contain electrodes placed blindly within the PSA[36] and that the actual location of the active electrode contacts of the DBS lead is seldom taken into consideration. Further, many reports lack a preoperative baseline and the results are often reported in a heterogenous manner, making comparison between different studies difficult[12, 18]. Regarding cZi DBS, excluding our own studies, the results of cZi DBS in 33 patients have been presented in five small and non-randomized studies[3]. Concerning the relative merits of the two targets, we have previously presented a tremor reduction of 86 % following cZi, compared to only 60% in the Vim[4], and demonstrated that the electrode contacts with the best effect in what was called Vim were often placed in the PSA[36]. There is further a scarcity of long-term data regarding both targets[1, 18].

Identifying the brain target in the individual patient

In a recent study of 28 000 procedures, electrode revisions constituted up to one third of all DBS procedures[35]. It is likely that misplaced electrodes due to difficulties in identifying the target is one of the major causes explaining a poor result in DBS for movement disorders[10, 38].

There are a number of different ways in which the target can be identified. Even for brain targets that can be visually identified on MRI, some centres rely mostly on statistical coordinates of the targets based on anatomical atlases, but this may result in poorly placed electrodes, due to significant inter-individual differences in the anatomy[25]. However, concerning the Vim, identification of that target in relation to ventricular landmarks is a necessity since the Vim cannot be visualized as such in MRI.

Currently, 60 % of the centres are relying on micro-electrode recording (MER) in order to identify the target in the individual patient. This is an invasive neurophysiological method necessitating considerable resources. It is also associated with an increased risk of haemorrhages, since it involves introducing several sharp cannulas and electrodes into the target area[39]. The third method is visual anatomical targeting, whereby the target is identified on the patients´ MRI, either directly or in relation to visible very closely related landmarks (Figure 2). We have over the years made significant contributions in the development of this last method, both concerning the pallidum[26], STN[22] and cZi[14, 36]. Unfortunately this method demands a high level of dedication and relies to a high degree on personal experience.

Scientifically based guidelines delineating the target areas and identifying the optimal target do not readily exist.
Common for all different methods is that it is normally required that the patient is awake during surgery in order to allow for intra-operative testing of effect/side effects, even if some today perform the procedure in general anaesthesia concerning some of the targets. If the brain targets could be identified with a high degree of certainty, and the electrode position within that target can be verified during surgery, then having the patients awake during surgery would no longer be necessary.

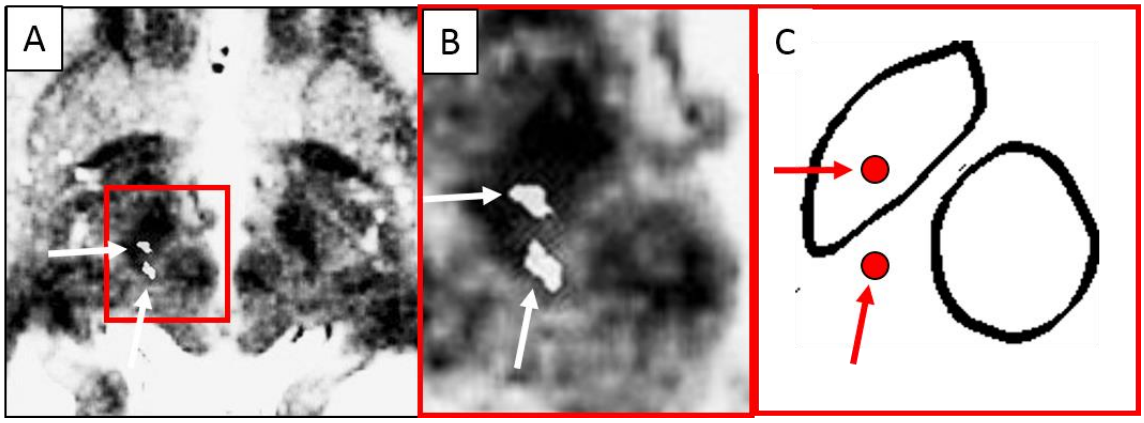


Figure 2). Example of visual anatomical targeting. In the enlarged MRI section (B) one electrode is place in the STN, and one electrode more posterior in the cZi. A schematic representation (C) demonstrate the relation of the electrodes to the STN and red nucleus.

Identifying and delineating the optimal targets
The literature regarding optimal target point/volume for the different targets is surprisingly meagre. The most common target, the subthalamic nucleus (STN), is also the most studied regarding this issue, but the effect has been evaluated in relation to the location of the electrode in no more than 260 patients in a total of 13 different studies[7]. Interestingly, most of these studies have found that the best effect is not achieved in the target structure itself, but in another adjacent structure, the more rostral part of the Zona incerta overlying the STN[7, 23, 33]. The same is true regarding the few studies of thalamic surgery for tremor, where most have demonstrated that the best effect is achieved from contacts outside the thalamic target, in the PSA[19, 24, 30, 32, 36]. Concerning other targets/indications the literature is even more limited.

The existing studies are further hampered by the heterogeneity of the methods. Often it is not the actual location of the electrode that is reported, but the intended one. Even when the actual location is reported it is most often presented according to distant landmarks, even if the targeting was done visually, which is a significant problem, taking into consideration the inter-individual variability. Further, even though the stimulation parameters used can differ widely and hence the electrical current affect different neighbouring structures, this is virtually never taken into account.

DBS for ET – Conclusions and aim
DBS for ET is thus not an evidence based therapy and the same is true regarding both target areas used for ET. The relative merits of the different targets used have not been clearly demonstrated and the individual targets are not well delineated. There is thus a need to address these issues.

PROJECT DESCRIPTION

Overview - What are we going to study?

The effect of DBS for ET will be evaluated in a multicentre study recruiting 100 patients randomized to immediate surgery (group A) or best medical treatment only (as decided by the movement disorder neurologist, with few exceptions likely to be identical to their current medication) with delayed surgery at 6 months if still needed /indicated (group B). Primary outcome is tremor reduction as measured with Essential tremor rating scale[11] (ETRS), with focus on items 5/6 (hand tremor) & 11-14 (hand function)[18], at baseline before surgery and at 6 months. Secondary outcome includes quality of life measured with QUEST[28] and electrical energy consumption[18]. After 6 months group B is operated –as indicated-, and group A and B are thereafter evaluated as one single group for long-term effects and analyses of electrode location. The electrodes will in all patients be inserted with a trajectory developed for this study allowing stimulation both in the established and traditionally used target Vim as well as in the new target cZi. Each contact will be evaluated individually concerning location, effects and side effects, in relation to stimulation parameters. This is done in order to, a) compare the two targets, but more importantly, b) to create a map of the whole area with identification/delineation of the optimal target point/volume. The time necessary to gather 100 patients is estimated to 2.5 – 3 years.

Study design:

- Step 1 is designed as a randomized controlled trial in order to compare the effect of DBS (Group A) and medical treatment (Group B) on ET (Aim 1).
- In step 2 – 4 the patients in group A are operated and group A and B joined into one single group.
    - Step 2 - all electrode contacts are individually analysed regarding chronic and acute stimulation effects in relation to their location in either the Vim or the cZi in order to decide which target is more effective (Aim 2).
    - Step 3 - Effects and side effects, with consideration to field of stimulation, are analyzed in relation to neighboring structures in order to map the whole area and delineate the optimal target points (Aim 3).
    - Step 4 - The long-term effect is evaluated in a non-randomized longitudinal study at 1, 3, 5, 10 years (Aim 4).
    -

Sample size and power:

In step 1, with a confidence interval of 95%, and an expected improvement of 85 % in the surgical group and none (or at least < 25%) in the medical group, regarding contralateral items 5/6 & 11-14, a power of 100 % is achieved. In step 2, with an expected improvement of 85% in one target and 60% in the other, a power of 98% is achieved. The high number of patients is, however, necessary for step 3, mapping of the area, in order to give a good cover of the periphery (Length of contact carrying electrode surface 7.5 mm, expected mean non-random intended deviation from target point (as defined in the study) 1 mm, expected mean random deviation from intended target point 1.5 mm)[40]. Based on the previous experience, less than 5% of patients is expected to be lost during the follow up, which will have an insignificant effect on the power.

Population

- ***Inclusion criteria***: Diagnosis of ET, as decided by the movement disorder specialist; Substantial incapacity; Duration of symptoms > 5 years; Age 18 – 75; unsatisfying effect from β-blockers, or be unable to tolerate the medical therapy.

- ***Exclusion criteria***: Cognitive impairment; Co-morbidity or non-compliance likely to jeopardize the result or to confuse the evaluation; Normal surgical exclusion criteria.

Endpoints

Primary outcome measure

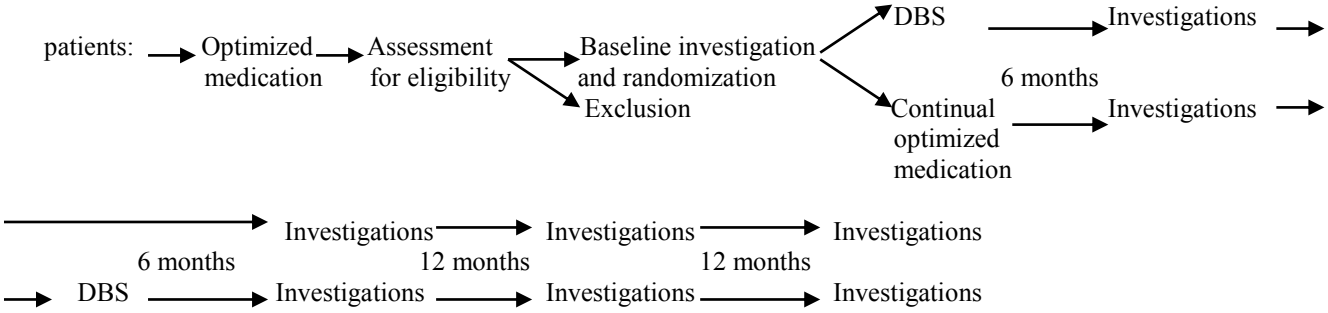
- ETRS[11]

Secondary outcome measures

- Quality of life in ET (QUEST)[28]
- Neuropsychological tests
- Electric energy consumption[18]

Chronology of assessments/investigations

ETRS, QoL, electric energy consumption: baseline, 6, 12, 24, 36, 48, 60, 120 months.
Neuropsychological tests: baseline, 12 months



Surgery

The patients are implanted using a trajectory targeting both the traditional target in the Vim and the new target in the cZi, with electrode contacts in both structures. Variations in the anatomy of the individual patient in combination with random deviations from the intended target point, will guarantee a spread of electrode contacts through the area of interest (Figure 3).

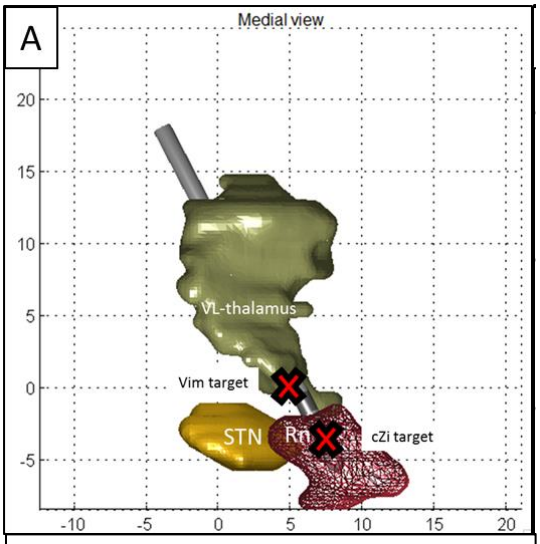
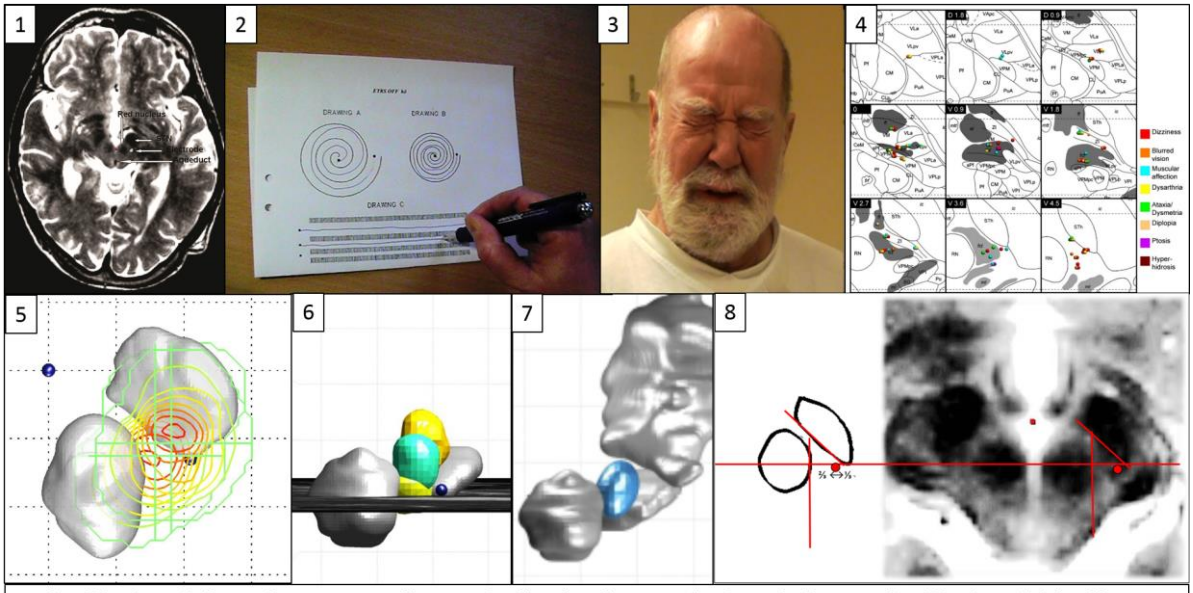


Figure 3. A Sagittal view an electrode with contacts in both the Vim and cZi. demonstrating the location of the two targets.

Evaluation of stimulation

Tremor is measured with ETRS[11] (with focus on items 5/6 (hand tremor) & 11-14 (hand function)[18]. ETRS is performed before surgery at baseline and at 6 months on/off med/stim. The evaluation is done blinded to the patients in the surgical group. The evaluation is documented on video (with the patient wearing a head cap) and segmented for blinded evaluation of two expert evaluators. In the second step all individual electrode contacts are evaluated in the same manner regarding tremor, but also regarding side effects, with standardized stimulation parameters and a gradual increase of voltage (Figure 4).



1. Identification of electrode contacts and anatomical landmarks. **2.** Evaluation of effect. **3.** Identification of side effects. **4.** Mapping of effect/side effects. **5.** Analysis of effect/side effects with consideration to field of stimulation. **6.** Creation of 3D-models of effects/side effects. **7.** Identification of optimal target volume based on effect/side effects. **8.** Creation of simple rules for identification of the optimal target based on the individual patients anatomy.

Figure 4. Target analysis

Target analysis

All individual electrode contacts are evaluated as described above (Figure 4). In all patients a preoperative MRI (with tractography) and a postop MRI/CT are performed under stereotactic conditions, allowing fusion of the images. The exact location of each contact is determined in relation to multiple neighbouring structures, among other structures, the anterior and posterior commissures, the center of the red nucleus, the posterior tip of the STN and the cerebellothalamic fiber bundle as identified on tractography. The analysis is performed using the Framelink navigation tool by two experts. The contacts are plotted on stereotactic atlases and 3D models created. The contacts are further classified according to their location and effects/side-effects. The electrical properties of the area surrounding each contact are analysed, and the stimulation parameters are documented in order to map the actual field of stimulation. Based on these data the different targets can be outlined with respect to optimal effects/lack of side effects and maps of the area created.

This is done to outline the optimal target, to provide a map for preoperative planning of the electrode location; to provide a map for interpretation of peroperative findings of macrostimulation and further to develop optimal stimulation strategies.

Further, we have within the EU FP-7 IMPACT project developed a computorized model with automatic segmentation of the target area based on the MRI of the individual patient for targeting and a stimulation model based on the location of the electrode. This model will in the current project be adapted to the VL-thalamus/PSA and tested against best clinical practice. Hopefully, this will be of help for the non-expert regarding targeting, and reduce the necessary time for optimization of stimulation parameters.

Statistics:

Two-tailed T-test will be used for continuous variables, Wilcoxon signed rank test for paired non-parametric data and Mann-Whitney U test for un-paired non-parametric data. The model of stimulation fields, Volumes of Neural Activation (VNAs), will be generated using simulations of homogeneous tissue with density compensated probabilistic stimulation

maps[14]. Registercentrum Norr will be responsible for the statistical analyses and stimulation field analysis will be done by Medtronic Eindhoven Design Center for Neuromodulation.

Organization

The international experience, as well as our own, has demonstrated that a study of this size necessitates a large population. The study will therefore be conducted on a national scale as a multicenter study including all six departments performing DBS surgery in Sweden, thus covering a population of 10 million inhabitants.

The work is coordinated by the Unit for Deep Brain Stimulation in Umeå, while strategic decisions are made by the steering group of the Swedish DBS study group: Umeå University Hospital – Patric Blomstedt, Professor in stereotactic functional neurosurgery, Marwan Hariz, Professor in functional neurosurgery. Linköping University Hospital - Peter Zsigmond, associate professor in neurosurgery. Sahlgrenska University Hospital - Thomas Skoglund, associate professor in neurosurgery. Karolinska Institutet - Anders Fytagoridis MD, PhD, neurosurgeon. Lund University Hospital - Anna-Lena Törnqvist, PhD, specialist nurse, Hjalmar Bjartmarz, neurosurgeon. Uppsala University Hospital - Nils Wesslén, neurosurgeon.

An internet-based register created and run by Registercentrum Norr in collaboration with us has been developed to function as a national quality register regarding DBS and as a research register for the current project. In order to ensure conformity in surgical techniques and evaluations we have developed an internet-based resource with targeting models and examples and we are providing on-site education regarding the items of importance. Further, in order to ensure conformity in targeting, as well as for evaluation of electrode location, we have also developed a technique for sharing of operation plans – "Tele-targeting".

Simulations of stimulation fields and creation of functional maps based on stimulation response and other information are being performed in collaboration with the Department of Biomedical Engineering at the University of Linköping and with the IMPACT-network (Umeå, Cologne, Germany & Salpetriere, Paris) led by Sapiens Steering Brain Stimulation.

PRELIMINARY RESULTS

We have in a number of previous studies evaluated DBS for ET in both the Vim and cZi[1-6, 14-16, 18, 20, 36]. These studies have analysed effects, complications, long-term outcome, quality of life and effects and side effects in relation to electrode location. Unfortunately, these are non-randomized and/or small studies. However, it seems quite clear that the effect of cZi DBS is promising: in a recently submitted manuscript about 50 patients we could demonstrate an improvement of contralateral tremor and hand function by 86% after 12 months. The contact evaluation demonstrated that the best effect was achieved within the target area itself, and that this target area is clearly distinct from the Vim. We have previously demonstrated in non-randomized longitudinal studies that the effect of cZi is superior to Vim DBS, where the tremor reduction in the latter target was only 60%[4], and that the electrode contacts with the best effect in what was called Vim were actually placed below the Vim, in the cZi area[36].

ETHICAL CONSIDERATIONS

Patients will be offered participation in this study only after the patient has been accepted for surgery with DBS. Thus, patients not included in this study will anyhow undergo the same

procedure. The surgery with combination of the two targets is an improvement of the procedure, which has been done since 2004 in Umeå. The evaluations performed before and after surgery are normal clinical practice and will not differ between patients participating in the study and patients not participating in the study. Minor differences in the evaluations exist today between the participating clinics, why minor changes of the standard clinical protocol will be necessary at some clinics.
The difference between normal clinical practice and this study is the randomisation into two groups, with immediate/delayed surgery. However, considering that the average waiting time for DBS is longer than 6 months, this does in reality mean that one of the groups will have a normal waiting time, while the other will have a shorter waiting time than normal. The patients who are randomized to delayed surgery will further have one additional evaluation (6 months after randomization) compared to a patient not participating in this study.

CLINICAL SIGNIFICANCE
The number of targets and indications for DBS is expanding rapidly. However, few indications and targets are evidence based. Considering that this is an invasive and lifelong treatment of high the cost it is desirable that all DBS procedures in clinical practice are evidence based.

In the current study the "established" target in the Vim will be compared with a new target in the caudal Zona incerta. Our previous studies have demonstrated the latter to improve tremor and hand-function with 86 %, compared with 60 % in the former. Further, the effect is in the former stable over time and the electric energy consumption is considerably lower, suggesting that the implant cost can be much reduced.

In the literature, the number of misplaced electrodes with non-optimal results and/or side-effects is high. Identification of the optimal target would yield better results, fewer stimulation programming sessions, and avoidance of expensive re-operations[9, 35].

OTHER GRANTS AND RELATED PROJECTS
Grant applications are planned to Vetenskapsrådet in 2018 for "Klinisk behandlingsforskning" and "projektbidrag".

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