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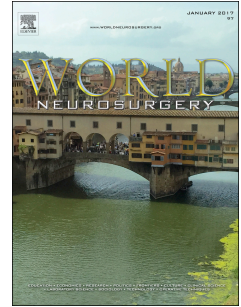
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DEEP BRAIN STIMULATION FOR ESSENTIAL TREMOR: A COMPARISON OF TARGETS

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ABSTRACT

Introduction

Deep Brain Stimulation (DBS) is an established treatment for refractory Essential Tremor (ET). Initially, the target of choice was the thalamic Ventral Inter Mediate nucleus (VIM). However, the Zona Incerta (ZI) has been put forward as a superior target. Both targets are considered safe and effective, but a direct comparison between these targets is lacking.

Methods

We analyzed a single-center cohort of 44 ET-patients treated with DBS between 1998 and 2017, targeting the VIM and/or ZI. Patient Reported Outcome (PRO) on the Washington Heights-Inwood Genetic Study of Essential Tremor rating scale (WHIGET), adverse events (AE) and Stimulation Induced Side-Effects (SISE) were assessed.

Results

The PRO of ZI-DBS (-2.2 ± 1.2 ; 18 patients with 28 electrodes) was superior to VIM-DBS (-1.2 ± 1.4 ; 10 patients with 19 electrodes) [$p < 0.01$]. There was no difference in AE between implantations in VIM (45%) and ZI (46%). Dysarthria SISE were significantly more reported after VIM-DBS [$p = 0.01$], while visual SISE occurred more often after ZI-DBS [$p = 0.04$].

Conclusion

In our study ZI-DBS was superior to VIM-DBS in terms of patient reported effectiveness. There was a comparable number of complications between both targets. This finding further advocates the ZI over the VIM as the principal DBS-target in ET.

INTRODUCTION

Essential Tremor (ET) is the most common movement disorder with a prevalence of 0.9% worldwide, increasing with age up to 21% in people over 95 years of age.¹ ET typically occurs in both upper extremities during specific actions or postures, sometimes with involvement of the head and vocal cords. Usually the course of ET is mild and can be managed with medication. However, in refractory cases, Deep Brain Stimulation (DBS) is a safe and effective therapeutic option.

The first anatomical target for DBS in ET was the thalamic Ventral Inter Mediate nucleus (VIM). Flora et al. reviewed 16 studies that showed a reduction of tremor after VIM-DBS, with an average reduction varying from 33.9 to 75.8%.² Although VIM-DBS still reduces tremor after more than 10 years,³ its long-term efficacy is decreased due to tolerance.⁴⁻⁸ Also, stimulation induced side-effects (SISE) such as gait ataxia, disequilibria and dysarthria often limit the therapeutic potential.^{2,9,10}

In 1972 Velasco et al. published pioneering work indicating the posterior subthalamic area (PSA) is of interest in surgery for tremor.¹¹ More recently, the Zona Incerta (ZI) and its neighboring anatomical structure, the prelemniscal radiation (RAPRL), both part of the PSA, have been proposed as (more effective) targets for DBS in ET. The clinical effect in these targets is proposed to be due to direct modulation of the dentato-rubro-thalamic tract (DRTT). In two case series, VIM targeted electrodes that turned out to stimulate the PSA were more effective than the electrodes that were actually in the VIM.^{12,13} In the first case series (n=6) reporting the ZI as a DBS-target an average tremor reduction of 81% was achieved at least six months after implantation.¹⁴

Hereafter, two more cohorts have been published: Plaha et al. report an average tremor reduction of 74% in a cohort of 15 patients and Blomstedt et al. report a 95% improvement in 21 patients.^{15,16} Three to five years after implantation, ZI-DBS is still effective and tolerance was “not apparent”.¹⁷ Even in patients with failed VIM-DBS, ZI-DBS still is reported effective.¹⁸

The SISE of ZI-DBS in ET include paresthesias, dizziness, visual complaints, muscular effects and dysarthria.¹⁹ No data on severity or percentage of SISE is available. Although tremor reduction with ZI-DBS is consistently reported higher than with VIM-DBS, no studies directly comparing these DBS-targets are available. A single report about both VIM-DBS and ZI-DBS unfortunately had to conclude that these cohorts were not comparable due to differences in follow-up and study design.²⁰ Thus, there is an unmet need for evidence on the most effective target for DBS in ET. In the present study, we compare the efficacy on a patient reported outcome scale and the incidence of complications and stimulation induced side-effects of ZI-DBS and VIM-DBS.

MATERIALS & METHODS

STUDY POPULATION

This retrospective study was performed at our University Medical Center. This cohort consists of 44 consecutive patients (93 electrode implantations) who underwent DBS for ET between 1998 and march 2017, targeting the VIM and/or ZI. Choice of target was era dependent: before 2004 VIM was the sole target, due to new insights in the field, from 2004 on the ZI was the primary target.¹⁴

All patients fulfilled the ET criteria of action tremor on predominantly the upper extremities; the final diagnosis was made by a movement disorders neurologist. Patients were considered eligible for DBS by our multidisciplinary DBS team if tremor was severely debilitating despite adequate medical therapy in the absence of contraindications for surgery. Patients who had either concurrent Parkinsonism or an earlier ipsilateral thalamotomy were excluded for this study.

SURGICAL TECHNIQUE

After application of the Leksell frame with localizing box, a CT scan was performed and fused to a preoperative 3T-MRI using BrainLab stereotactic planning software. The DBS-targets VIM and ZI were determined using both a direct visual planning method as well as an indirect planning methods using distance to mid commissural point (MCP). DBS electrodes (Medtronic lead type 3389) were implanted under local anesthesia. After electrode implantation, intra-operative clinical testing of the stimulation effect and SISE was performed. During the same surgical procedure, the implantation of an Internalized Pulse Generator (Medtronic) was performed under generalized anesthesia. From 2006 on (58/93 electrodes) stereotactic postoperative imaging was available for analysis of accuracy.

OUTCOME

The primary outcome measure was tremor reduction of the contralateral upper limb as Patient Reported Outcome (PRO) on the 5 point Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) rating scale,²¹ in which 0 represents no tremor and 4 represents severe tremor (e.g. unable to drink anything from a glass). WHIGET

scores of the situation before and after DBS implantation were obtained after DBS implantation.

Complications were recorded from the patient file and divided in early (<1 month after implantation) and late AE and SISE. Tolerance to DBS was defined as recurrence of tremor at least one year after the DBS implantation for which the stimulation parameters needed to be increased.

STATISTICAL ANALYSIS

WHIGET tremor reduction scores were compared using the Mann-Whitney-U test between targets, and using the Wilcoxon rank-sum test within targets. Differences in categorical variables were analyzed using the chi-square or Fisher's exact test. For continuous variables, the t-test or Mann-Whitney-U test was used. For correlations between continuous and ordinal data Spearman's rho was calculated. Averages are reported as mean \pm SD. Effect sizes were reported using Cohen's D. Testing was performed two-sided (using IBM SPSS statistics 24) and $p < 0.05$ (unrounded) was considered statistically significant.

ETHICS

All implantations were performed in a care-as-usual setting. According to Dutch legislation no ethical approval was necessary for the study, which was confirmed by our local research ethical board (REB decision 2015/132).

RESULTS

Our cohort of 44 patients consisted of the following DBS implantations: unilateral VIM (8%), unilateral ZI (6%), bilateral VIM (30%), bilateral ZI (44%) and ZI in one hemisphere and VIM in the other (12%). Six patients were operated twice: three patients with 5 ZI electrode implantations previously underwent unsatisfactory VIM-DBS, and three VIM patients (5 electrodes) previously underwent unsatisfactory VIM-DBS (2 electrodes) or ZI-DBS (3 electrodes). This adds up to a total of 50 operations with 93 electrodes implanted (42 VIM and 51 ZI) (**Error! Reference source not found.**).

Patient characteristics are shown in **Error! Reference source not found.** The mean interval between surgery and evaluation was the only significant difference ($p < 0.01$) between the VIM group (9.3 ± 1.1 years) and the ZI group (4.6 ± 0.5 years). Nevertheless, follow-up duration did not correlate with tremor reduction ($\rho = -0.19$; $p = 0.22$).

STEREOTACTIC TARGETING

For the VIM, the target coordinates (mm to AC, lateral = x, posterior = y, inferior = z) were: x: 15.4 ± 1.4 y: 16.5 ± 1.7 z: 3.7 ± 0.7 . For the ZI coordinates were: X 10.5 ± 0.9 y: 19.3 ± 1.6 z: 4.3 ± 1.0 . All implantations had their entry point (burr hole) close to the coronal suture on the ipsilateral side. The deviation from target (in mm) was similar for the VIM (1.4 ± 0.5) and ZI (2.2 ± 1.0 ; $p = 0.76$). For the ZI group the z coordinate showed a significant correlation with tremor reduction ($\rho = 0.37$; $p = 0.05$, Figure 1), with more

inferior electrodes showing a better PRO. For the VIM group, too limited data was available (4 electrodes) to perform these analyses.

Coordinates of the center of the stimulation field were (mm to MCP) ZI: $x = 9.4 \pm 2.1$ $y = 6.9 \pm 1.2$ $z = 3.4 \pm 1.4$, VIM: $x = 14.8 \pm 2.1$ $y = 4.7 \pm 0.7$ $z = -2.5 \pm 1.8$.

TREMOR REDUCTION

In 48 (19 VIM / 29 ZI) out of 93 electrodes sufficient data was available for the comparison of tremor reduction. Missing data was due to: a deceased patient (unrelated to DBS or ET), surgery after evaluation, unreachable by telephone, depleted battery, DBS removal or too much deviation from the intended target (more than three times the median deviation).

The baseline WHIGET tremor scores for the contralateral arm were equal for VIM (3.8 ± 0.4) and ZI electrodes (3.7 ± 0.7 ; $p=0.89$). Results improved significantly from baseline in both the VIM (-1.2 ± 1.4 ; $p<0.01$) and ZI (-2.2 ± 1.2 ; $p<0.01$) group. Improvement was superior in the ZI group (Cohen's D: 0.77; effect-size: 0.36; $p=0.02$).

COMPLICATIONS

Six of the 50 implantations were excluded from complication and side-effect analyses because they had both VIM and ZI leads implanted. Except when mentioned explicitly, all complications were reported to have improved or did no longer require medical attention.

Early Adverse Events

Nine of 19 VIM implantations had early AE vs. 11 of 25 ZI implantations ($p=0.96$). The most common AE was postural instability/gait ataxia (1 VIM, 4 ZI; 2 ZI cases were permanent); dysarthria (2 VIM, 5 ZI); delayed wound healing/wound hematoma (5 VIM, 3 surgical revisions); and eyelid edema (2 VIM). The following AE occurred only once: intracranial hemorrhage with hemi-paresis and epilepsy (ZI, largely recovered); epileptic seizure (VIM); small hematoma in the ZI leading to dysphasia (ZI); deep venous thrombosis (VIM); and hypertension (ZI).

Late Adverse Events

AE reported during follow-up were: unpleasant sensation/pain at the internalize pulse generator or extension cable (4 ZI, 2 VIM, 3 requiring re-operation); DBS removal due to infection (1 VIM, 1 ZI); hoarseness (1 ZI); and dysphagia (1 ZI).

Stimulation Induced Side-Effects

One ZI case was excluded for SISE analysis, because the DBS system was never activated due to a persistent microlesion (stunning) effect. Two cases (5%) report no SISE (1 VIM, 1 ZI). Stimulation-induced dysarthria was reported significantly more often in patients with VIM-DBS (75%) than with ZI-DBS (39%; $p=0.02$), whereas more patients with ZI-DBS (46%) than VIM-DBS (16%) reported visual SISE ($p=0.04$). There was no difference in motor, sensory, psychological, seizure or other SISE categories (Table 3).

Tolerance

A total of 22 patients (7 VIM, 15 ZI) were available for analysis of tolerance. Tolerance occurred in all VIM-DBS cases and 42% of the ZI-DBS cases ($p=0.02$). However, follow-

up correlated with the occurrence of tolerance (ρ : 0.59; $p < 0.01$) and the follow-up in the VIM group was significantly longer than the ZI group (as reported above).

DISCUSSION

TREMOR REDUCTION

Our data show that both ZI-DBS and VIM-DBS are effective and safe therapies for ET. The tremor reduction of 32% (VIM) and 59% (ZI) is in line with previous reports on the effectiveness of DBS in these targets.^{2,4,17} The higher tremor reduction in the ZI group confirms the alleged superiority of this target²⁰, but it should be noted that in this study a PRO was used instead of a clinical rating scale. Our average coordinates for the center of the stimulated field in the ZI are in line with other publications that reported these parameters.^{14,16} The correlation with tremor reduction of the z coordinate in the ZI group is interesting, since at the level of the ZI the DRTT is virtually horizontally oriented and therefore very sensitive to deviations in this plane.²²

COMPLICATIONS AND STIMULATION INDUCED SIDE-EFFECTS

Our number of complications is comparable to the number (50%) published by Fytagoridis et al., although we mainly encountered dysarthria and postural instability instead of dysphasia.¹⁹ This may be due to a reporting bias or a difference in diagnostic/classification criteria. Fytagoridis et al. 2013 were the first to give a comprehensive overview of SISE of ZI stimulation.²³ Our study reports a lot more SISE, but we reported all SISE instead of just the ones limiting programming.

This study is the first to directly compare SISE between VIM and ZI. And interestingly a different profile of SISE was found. Where VIM stimulation more often induced dysarthria, ZI stimulation showed more visual SISE. This might be due to the different anatomical location, with a bigger distance to the internal capsule but smaller distance to the optic tract. However, a recent publication about SISE in the PSA could not relate SISE to anatomical location.²³

Our results might indicate less tolerance for the ZI. However, the difference in follow up confounds this effect. And our definition of tolerance (increase in stimulation parameters after one year) is broader than the definition other authors used. Therefore, a comparison is impossible. The authors would be interested in inclusion of this parameter in a future study.

LIMITATIONS

The major limitation of our study is its retrospective design, which makes our data vulnerable to bias. We attempted to minimize reporting bias by including all consecutive patients. Another limitation is the difference in implantation era between targets. Since imaging techniques improved and DBS has a learning curve there might be a bias. However, the surgical accuracy is equal between groups, the time since surgery did not correlate with PRO and the same DBS team is still responsible for continuously optimizing stimulation parameters in both groups. Therefore, we consider the risk of bias minimal.

FUTURE DIRECTIONS

A randomized controlled trial is needed to carefully evaluate the potential benefit of ZI-DBS over VIM-DBS. The design of Barbe et al. 2016 is very promising in its attempt to use a single electrode to potentially stimulate both the VIM or ZI.²⁴ And a cross-over design is planned to directly compare both targets within each patient. Since the effect in both targets may come from modulating the DRTT, another interesting development is directly targeting the DRTT.^{25,26}

CONCLUSION

In our cohort ZI-DBS was superior to VIM-DBS in terms of patient reported outcome with a comparable number of complications. This further advocates the ZI over the VIM as the principal target for DBS in ET.

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Figure 1 shows the x, y, and z coordinates (mm to AC) for each ZI electrode in relation to the achieved PRO (tremor reduction in points on the WHIGET scale). Higher z coordinates showed a better PRO (rho: 0.37; p=0.05).

ACCEPTED MANUSCRIPT

TABLE 1 IMPLANTATIONS AND ELECTRODES.

	VIM	ZI	VIM + ZI	Total
Implantations	19*	25 [†]	6	50
Unilateral Implantations	4	3	x	7
Bilateral Implantations	15	22	6	43
Electrodes	42	51	x	93

* 1 patients underwent two bilateral VIM implantations; 2 patients previously underwent ZI implantation. † 3 patients previously underwent VIM-DBS. In total 44 individual patients.

TABLE 2 PATIENT CHARACTERISTICS

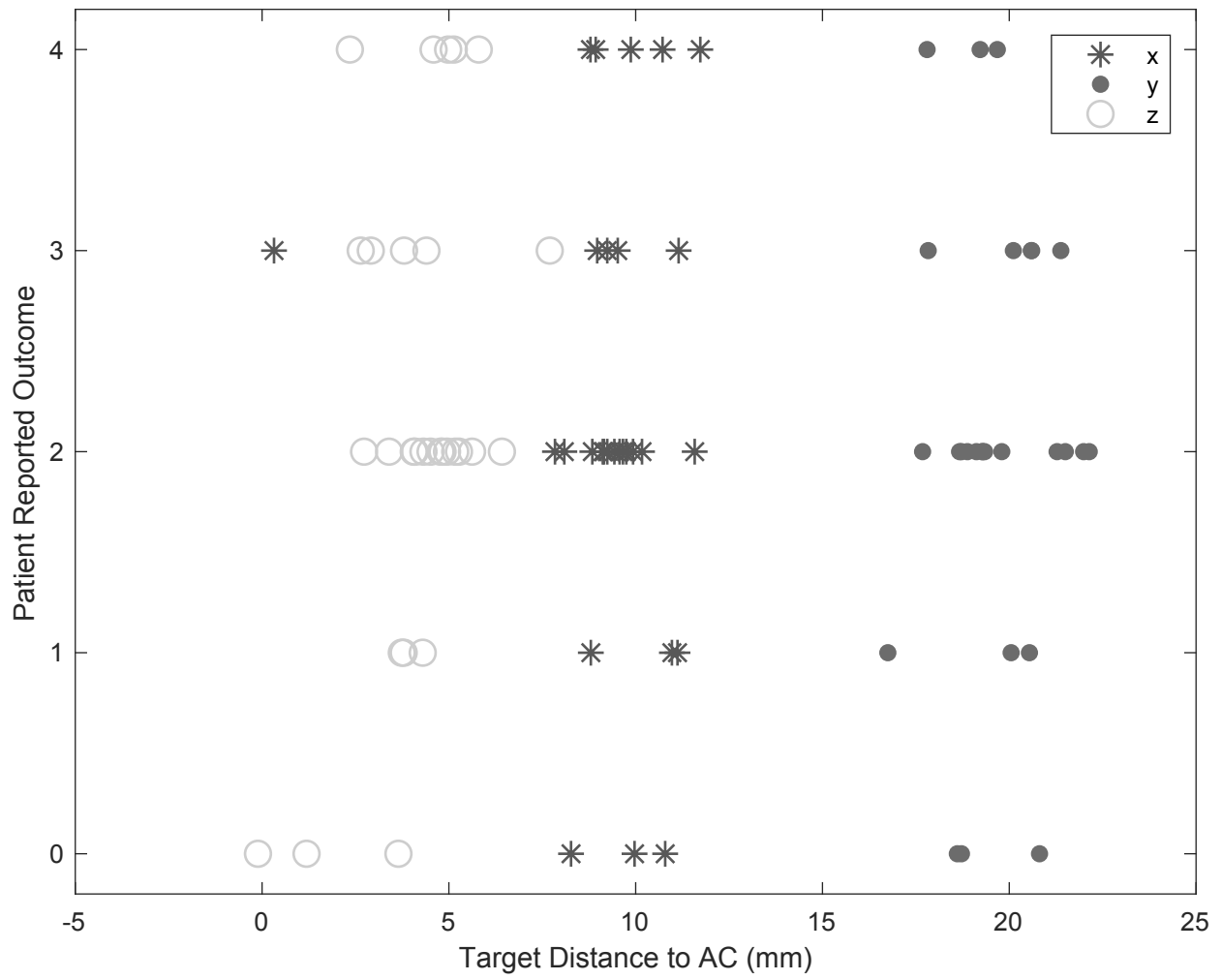
	VIM	ZI	VIM vs ZI (<i>p</i>)
Male Sex	74%	65%	0.35
Age at onset of symptoms	38±22	42±19	0.44
Age at surgery	42±10	51±9	0.85
Years between onset and surgery	25±14	28±17	0.31
Unilateral procedures*	21%	12%	0.44
On medication at analysis	20%	26%	0.66
Follow up (years)	10.6±4.5	5.8±3.0	<0.01
Target deviation (mm)	1.4±0.5	2.2±1.0	0.76
Stimulation voltage	2.4±1.0	2.4±0.9	0.90
Stimulation frequency (Hz)†	184±1.6	177±19	0.06
Stimulation pulse width (µs)†	73±15	70±17	0.40
Mono polar stimulation	47%‡	42%§	0.74

*6 right sided, 1 left sided implantations. †6 ZI electrodes were excluded: 2 batteries were depleted, 4 had adequate tremor control without stimulation. ‡ 6 bipolar, 4 tripolar, § 12 bipolar, 2 tripolar

	VIM	ZI	VIM vs ZI (<i>p</i>)
WHIGET Contralateral Arm*			
-Preoperative	3.8±0.4	3.7±0.7	0.89
-Postoperative	2.6±1.3	1.5±1.1	0.02
-Improvement	1.2±1.4 (<i>p</i><0.01)	2.2±1.2 (<i>p</i><0.01)	0.02
Tolerance [‡]	100%	42%	0.02
Early AE [†]	45%	46%	0.96
Late AE [†]	16%	16%	1.00
SISE [‡]			
-Motor	74%	50%	0.12
-Sensory	53%	50%	0.86
-Dysarthria	79%	38%	0.01
-Psychological	11%	4%	0.58
-Oculomotor/Visual	16%	46%	0.04
-Seizure	11%	0%	0.19
-Other	26%	13%	0.08

TABLE 1 TREMOR REDUCTION, TOLERANCE AND COMPLICATIONS

Data is from *19 VIM and 29 ZI electrodes, †19 VIM and 25 ZI implantations, ‡ 7 VIM and 15 ZI implantations.



Highlights

Deep Brain Stimulation for Essential Tremor: a Comparison of Targets

- Zona Incerta is the superior target in Deep Brain Stimulation for essential tremor.
- Ventral Intermediate Nucleus or Zona Incerta implantation has equal complications.
- Zona Incerta stimulation induces more visual side-effects.
- Ventral Intermediate Nucleus stimulation induces more dysarthria.

Abbreviations

Deep Brain Stimulation for Essential Tremor: a Comparison of Targets

AC: anterior commissure

AE: adverse events

DBS: Deep Brain Stimulation

DRTT dentato-rubro-thalamic tract

ET: Essential Tremor

MCP: mid commissural point

mm: millimeter

PRO: Patient Reported Outcome

RAPRL prelemniscal radiation

SD: standard deviation

SISE: Stimulation Induced Side-Effects

VIM: Ventral Intermediate Nucleus

WHIGET: Washington Heights-Inwood Genetic Study of Essential Tremor

ZI: Zona Incerta

Conflict of interest statement

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