Essential tremor (ET) is the most common movement disorder in adults with an estimated prevalence of up to 5%. It is clinically characterized by kinetic tremor in the upper limbs, although similar symptoms may also affect different body regions in the same patient. ET has a complex pathophysiology, which has been classically attributed to abnormally synchronized neuronal oscillations in the inferior olivary nucleus. This pathological activity is believed to propagate via climbing fibers to Purkinje neurons of the cerebellar cortex and
from cerebellar nuclei to the ventral intermediate nucleus (VIM) of the thalamus and the motor cortex via the dentatorubrothalamic tract (DRTT). Because medical treatment is either ineffective or burdened by tolerable side effects in almost 50% of patients with ET, surgical lesioning of the thalamic nuclei used to be performed to achieve better tremor control. Once Benabid et al. demonstrated successful tremor control in 6 patients with ET who underwent deep brain stimulation (DBS) targeting the VIM, this surgical intervention was rapidly adopted by many centers worldwide because of the less invasive and reversible mechanism of action. Nevertheless, thalamotomies continued to be performed in poor surgical candidates using radiosurgery* and underwent a renaissance after the introduction of MRI-guided focus ultrasound. However, the VIM is not the only target investigated for tremor control in patients with ET.

In fact, variously placed subthalamicotomies for this purpose were reported in the literature between 1950 and 1970 and excellent results from DBS targeting the posterior subthalamic area (PSA) have been described in a growing number of modern studies. The PSA is a narrow anatomical zone, bounded by many relevant structures—anteriorly by the subthalamic nucleus (STN), posteromedially by the red nucleus, posteriorinferiorly by the medial lemniscus, laterally by the posterior limb of the internal capsule, superiorly by the VIM, and inferiorly by the substantia nigra. The caudal zona incerta (cZI) and the prelemniscal radiation (Rap1) are the two main structures within the PSA, but different groups preferred to target either one of these two structures, or PSA more generally. Furthermore, neither PSA component is clearly distinguishable on MRI* and their stereotactic coordinates given in the literature are heterogeneous. Some authors recently sustained the superiority of DRTT direct stimulation for tremor control in patients with ET. To disentangle the debate about the optimal target for tremor control, we analyzed a cohort of patients with ET after VIM-DBS and studied the location of the active contact in relation to the VIM, DRTT, and cZI. By doing so, we tried to understand which anatomical structure may mediate tremor control after the surgery and whether the same structure is also responsible for the ongoing clinical benefit years later after lead implantation.

Methods

Patient Selection

We retrospectively reviewed the clinical database of the University of California, Los Angeles (UCLA), Ronald Reagan Medical Center and searched for patients experiencing ET who underwent VIM-DBS between 2014 and 2022. All patients failed to reach satisfactory tremor control after treatment with both propranolol and primidone. As a standard of care, all patients underwent initial screening for VIM-DBS surgical candidacy by an experienced neurologist at the UCLA Movement Disorders Clinic. Elected candidates underwent additional screening by an experienced board-certified neurosurgeon at the Functional and Restorative Neurosurgery Program at UCLA Ronald Reagan Medical Center. For the pres-ent study, we included only patients whose clinical and imaging data necessary for electrode reconstruction were available in our database. This study was approved by the IRB of UCLA.

Surgical Technique

Informed written consent for the surgical procedure was obtained from all patients or their legally authorized representatives in accordance with the Declaration of Helsinki. Preoperative surgical targeting of the VIM was conducted indirectly according to stereotactic coordinates previously reported in the literature: 10.5–11 mm lateral to the wall of the third ventricle, 25% of anterior commissure–posterior commissure distance anterior to the posterior commissure, and 0 mm from the intercommissural plane. The lead trajectory was then planned on a post–contrast-enhanced T1-weighted MRI sequence. Before surgery, a Leksell stereotactic frame (Elekta) was placed on the patient’s head under general anesthesia and a stereotactic CT scan was obtained. In a dedicated workstation (Elements, Brainlab), the CT scan was coregistered with MRI sequences containing the stereotactic plan. The preoperative surgical target was planned to coincide with the second dorsal contact of the stimulating electrode. Infinity 4-channel leads (no. 6167–6169) or Infinity directional leads (no. 6171–6163; Abbot/St. Jude) were implanted after an attending neurologist confirmed a satisfactory clinical response. The lead would have been moved from the initially planned target based on awake intraoperative macrostimulation. Specifically, the lead was moved 1–2 mm inferiorly if the stimulation of all 4 contacts resulted in insufficient tremor control. In the case of persistent tremor after rostral electrode advancement, the lead was relocated anterior to the previous one. Conversely, the lead was placed more anteriorly for persistent unpleasant paresthesia or more medially for internal capsule side effects. No microelectrode recordings were performed during the surgery. The intracranial electrodes were connected to an Infinity internal pulse generator (IPG; Abbot/St. Jude) implanted in the right hemithorax. The IPG was activated 3 weeks after the implantation and the stimulation parameter settings were adjusted during the following outpatient clinics.

Lead Reconstruction and Localization

DBS electrodes were localized using the advanced processing pipeline in Lead-DBS (version 2.6, www.lead-dbs.org), as described in previous studies. Briefly, the postoperative CT image was linearly coregistered to the preoperative structural MR image using advanced normalization tools (ANTS) and brain shift correction was applied as implemented in Lead-DBS. All preoperative volumes were used to estimate a precise multispectral normalization to Montreal Neurological Institute (MNI) International Consortium of Brain Mapping 2009b NLIN asymmetrical space using the ANTs diffeomorphic mapping. DBS contacts were automatically prereconstructed using the phantom-validated and fully automated precise and convenient electrode reconstruction for DBS (PaCER) method or the TRAC/CORE approach and manually refined when appropriate. The resultant elec-

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trode models were then warped into the MN1152 NLIN 2009b asymmetrical space. Atlas segmentations in this paper are defined by the Essential Tremor Probabilistic Mapping Atlas to visualize the VIM and DRTT and the Zona Incerta Atlas to visualize the cZI. The Lead-Group tool in Lead-DBS was used for group visualization and to calculate the millimeter distance between the center of gravity of the active contact (gAC) of each patient’s electrode and the nearest voxel center of the VIM, DRTT, and cZI, as depicted by the respective atlases. For a subgroup of patients, the active contact was changed as of the last follow-up visit to achieve better tremor control. Therefore, gAC-VIM, gAC-DRTT, and gAC-cZI distances were recalculated for the electrodes for these patients according to the new active contact location.

Statistical Analysis

Demographic characteristics were reported using descriptive statistics, frequencies, and percentages. Continuous variables were reported as means ± standard deviations and categorical variables as absolute numbers and percentages. A Shapiro-Wilk normality test was used to assess normality across selected variables along with a close inspection of the data plotted on histograms and Q-Q graphs. Because active contact target measures were found to be nonnormally distributed overall, Friedman’s ANOVA was used to compare the mean gAC-VIM, gAC-DRTT, and gAC-cZI distances across all electrodes. The Wilcoxon signed-rank test was used to follow-up pairwise comparisons.

We then divided patients’ electrodes into two groups: electrodes whose location was changed based on intraoperative stimulation testing and electrodes that were implanted at the initially planned stereotactic target. MANOVA was used to perform multivariate comparisons in gAC-VIM, gAC-DRTT, and gAC-cZI distances between these two groups. In this context, the Pillai-Bartlett trace (V) multivariate test was used to test for overall statistical significance among all variables. In the case of multivariate significance, the ANOVA univariate F-statistic was chosen to perform follow-up tests. For the subgroup of electrodes whose active contact was changed at the last follow-up visit, Friedman’s ANOVA and follow-up Wilcoxon signed-rank test were used to access multiple pairwise differences between the mean gAC-VIM, gAC-DRTT, and gAC-cZI distances before and after active contact change. For all traditional hypotheses, p values < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS (version 28.0, IBM Corp.).

Results

Clinical Characteristics of Patients with ET

Forty-one patients with ET were selected for this study; 21 (51.22%) of 41 were female. The mean age at tremor onset was 36.17 ± 16.67 years, whereas the mean age at implantation was 64.5 ± 12.3 years. The mean Clinical Rating Scale for Tremor Part A score before the surgery was 36 ± 18.46. Twenty-seven (65.85%) of 41 patients were bilaterally implanted and 12 (29.27%) of 41 patients with unilateral implantation received left-sided VIM-DBS.

Active Contact Distance After Implantation

Sixty-eight electrodes were included in the analysis (Fig. 1A). The mean distances of the active contact center from the atlas structures were statistically significantly different (χ² = 80.67, p < 0.001). The follow-up pairwise comparison test confirmed that the mean distance of the center of the electrode’s active contact from the VIM (0.622 ± 0.9 mm) was significantly less than the mean distance from the DRTT (1.216 ± 0.141 mm, p = 0.008) and from the cZI (6.35 ± 3.67 mm, p < 0.001). Moreover, the gAC-cZI distance was also significantly higher than the gAC-DRTT distance (p < 0.001; Fig. 2A).

Twenty (29.41%) of the 68 electrodes were relocated after intraoperative macrostimulation. When dividing the electrodes based on this target change, the multivariate test did not find any overall differences in the two groups (V = 0.037, F[3,64] = 0.828, p = 0.483). In fact, both moved electrodes and the ones implanted in the preoperative target displayed a similar shorter gAC-VIM distance (mean 0.552 ± 0.487 mm vs 0.651 ± 1.026 mm) than both the gAC-DRTT (mean 1.453 ± 0.325 mm vs 1.117 ± 0.147 mm) and gAC-cZI (mean 5.68 ± 3.627 mm vs 6.627 ± 3.7 mm) distances (Fig. 2B).

Active Contact Distance at the Last Follow-Up

Sixteen (39%) of the 41 implanted patients had the active contact changed at the last follow-up visit (mean follow-up duration 37.5 months). These patients had > 50% tremor reduction with parameter optimization after the implantation, but they experienced progressive tremor recurrence until stimulation-induced tremor reduction was < 50% and active contact change was deemed necessary at the last follow-up visit. Eighteen active contacts were included in this subanalysis (Fig. 1B).

Statistically significant differences were found in the mean distances of the active contact center from the atlas structures (χ² = 53.35, p < 0.001). The Wilcoxon signed-rank test confirmed that the mean gAC-VIM at the last follow-up (0.803 ± 1.287 mm) was significantly shorter than the mean gAC-cZI distance (8.061 ± 3.44 mm, p < 0.001). Similarly, the DRTT was significantly closer to the active contact at the last follow-up (mean 0.4 ± 0.063 mm) than the cZI (p < 0.001). Although the pairwise comparisons were not statistically significant, the mean gAC-DRTT distance was reduced at the last follow-up compared to the same measure shortly after the implantation (0.4 ± 0.27 mm vs 1 ± 0.8 mm) and was also less than the gAC-VIM both before (mean 1.018 ± 1.435 mm) and after the active contact change. A more detailed description of the multiple pairwise comparisons is reported in Fig. 3.

Discussion

In the present study, we compared the distance of the center of the active contact from the target structures assumed to be involved in tremor control. During the first programming session after implantation, the active contact was significantly closer to the VIM than both the DRTT (p = 0.008) or the cZI (p < 0.001). However, stereotactic targeting of the VIM is still performed indirectly according to standard stereotactic coordinates adapted...
to the patient’s own anatomy, as for other thalamic nuclei due to the homogeneous appearance of the thalamus in the MRI sequences commonly used in clinical practice. Therefore, we perform awake macrostimulation to quantify tremor reduction and side-effect thresholds; hence, the preoperatively planned target may not coincide with the most clinically beneficial location where the definitive electrode will eventually be implanted. In this context, it has been reported that stimulation below the intercommissural line is clinically more efficient when aiming to target the VIM. Because the PSA is located below the intercommissural line and ventral to the VIM, some groups tried to target this area and reported tremor improvement as high as 87% after 1 year and up to 91.8% after 5 years in open-label studies. The ZI is a small nucleus mainly composed of gamma-aminobutyric acidergic neurons and occupies the dorsal and posterior aspects of the STN, lying between the Forel H1 field dorsally, H2 ventrally, and H medially. The ZI is classically divided into rostral and caudal components, both having extensive connections with the cerebral cortex, basal ganglia, cerebellum, brainstem reticular formation, and thalamic nuclei. While the rostral ZI appears to be involved in emotional and cognitive functions, the caudal or cZI is known to participate in the generation of gamma-band thalamocortical rhythms during motor tasks by gating unwanted sensory inputs via thalamic neuron inhibition. Based on these assumptions, a putative role of the cZI in the aberrant oscillatory activity underlying ET and Parkinson’s disease tremors does not seem unrealistic. Some authors have proposed the cZI as the main structure responsible for tremor control after PSA-DBS. Nonetheless, we performed a subgroup analysis and showed that there was no statistical difference in active contact distance from the three structures between electrodes relocated and electrodes implanted in the preoperatively planned target after intraoperative macrostimulation, since active contacts in both groups were always closer to the VIM than the cZI. Indeed, the intraoperative macrostimulation in our series actually led the active contact nearer to the VIM.

An acknowledged issue related to VIM-DBS is habituation, initially described by Benabid et al. as “tolerance” leading to a perceived reduction of clinical benefit in a variable proportion of patients ranging from 0% to 75%. In contrast, a less rapid decline in the clinical benefit of
the stimulation has been reported as a major advantage of PSA-DBS.\textsuperscript{42,43} To account for this clinical phenomenon, we reviewed the distance from the three investigated structures in patients in whom the active contact had changed at the most recent clinical follow-up programming. When analyzing this subcohort of electrodes, the gAC-VIM distance was still significantly less (p < 0.001) than the gAC-cZI distance. Therefore, the VIM was still more likely the best location for tremor control compared with the cZI at the last follow-up. Our results are consistent with recent work by Eisinger et al.,\textsuperscript{44} who showed that stimulation of contacts mapped closer to the VIM led to a better outcome than the ones of the same lead but closer to the PSA, even 4 years after the surgery. More interestingly, the gAC-DRTT distance was reduced at the last follow-up as was the gAC-VIM distance.

We performed a subanalysis on patients who needed stimulation parameter changes many years after the implantation to maintain tremor control. For these subjects, a more ventral contact was selected and used preferentially for stimulation as it yielded more effective tremor reduction. Interestingly, the new contacts were still in the VIM but closer to the DRTT, perhaps on the inferior border of the nucleus. Our finding suggests that the increased proximity of the presumed stimulation field toward the DRTT contributes to tremor control maintained after active contact change. The concept that a shorter distance from the DRTT correlates with better tremor control is not new in

FIG. 2. Results from multiple pairwise comparisons and subgroup analysis in patients with ET after the implantation. A: Bar chart describing the distance in mm from the gAC for each of the three target structures. The asterisk indicates statistical significance (p < 0.05 with the significant values adjusted by the Bonferroni correction for multiple tests) of the pairwise comparisons from the follow-up Wilcoxon signed-rank test. B: Multivariate comparison of the gAC distances of the three structures between electrodes implanted into and electrodes moved relative to the preoperative target after intraoperative macrostimulation. NS = nonstatistically significant (p > 0.05).
the literature—Coenen et al. have speculated that proximity to the DRTT might underlie the less severe habituation effect and the presumed superior antitremor benefit of PSA-DBS. The Rapl within the PSA is a heterogeneous structure, composed of fibers from the mesencephalic reticular formation, and the pallido-thalamic and cerebello-thalamic pathways. Targeting the DRTT fibers while still packed within the PSA before fanning out into the VIM would then cause a more extensive activation of this white matter bundle. Nevertheless, the fibers proper to the DRTT are hard to dissect from the other Rapl components even using the most advanced tractographic algorithms, although modern directional stimulating leads have been presented as a possible solution to address this issue in clinical practice.

Limitations of the Study

The reduced number of patients included in the follow-up analysis may have limited our results. We are confident that the shorter distance of the active contact from the DRTT than the VIM would have reached statistical significance with the inclusion of more subjects. Furthermore, the process of nonlinear registration from the patient’s native space to standard MNI space could theoretically induce inaccuracies in the localization of the three anatomical targets (VIM, DRTT, and cZI). However, the nonlinear registration algorithm implemented in Lead-DBS has been extensively validated with demonstrated submillimeter accuracy in many publications. Additionally, previous research attempted to map electrode location relative to MRI-invisible structures such as the cZI and Rapl by using commercially available planning systems.

FIG. 3. Detailed description of the multiple pairwise comparisons of the distances from the active contact at the last follow-up. A: Bar chart describing the distance (in mm) from the gAC for each of the three target structures before and after programmatic active contact changes. Overall statistical significance (p < 0.001) resulted from Friedman’s ANOVA test. B: Results from the follow-up Wilcoxon signed-rank test accessing statistical significance across the multiple pairwise comparisons. On the left, the numbers in the light blue cells indicate the significant values adjusted by the Bonferroni correction for multiple tests that rejected the null hypothesis, i.e., the two means were the same. On the right, the Z values correspond to the magnitude of the difference between the means of the pair distributions. Small, medium, and high differences between the means of the pair distributions are color coded in yellow, light red, and dark red, respectively.
software or classic stereotactic atlases thus our analysis based on validated MNi atlases may be considered more advanced. On the other hand, the distance from the active contact might seem to be a surrogate marker of target structure stimulation if it is compared with the surface covered by stimulation volume. Nevertheless, classic models of volume of tissue activated (VTA) generation are derived from VTA-radius, which is defined as the voxel distance to the center of the active contact and is proportional to the intensity of stimulation. Moreover, mathematical models of neuron response to stimulation showed that the distance from the active contact was an important determinant of the numbers and types of activated axons. Finally, a direct comparison between VIM and cZI surgical targets could not be completely inferred from our study, as also stated by Eisinger et al. in their work, because of the different surgical strategies needed for the two stereotactic targets. Our patients received only VIM-DBS and the planned target was based on a trajectory that might not have allowed a precise targeting of the structures within the PSA, according to technical studies focused on this narrow anatomical area.

Conclusions

By using the distance from the active contact as a measure of effective stimulation, our study demonstrated that the VIM itself is the structure that drives the anti-tremor effect of VIM-DBS even after years of stimulation. Conversely, the proximity to the DRTT demonstrated a promising role in maintaining the clinical benefit at later follow-up. Rather than the DRTT being the only target as sustained by other authors, we propose that direct visualization of the DRTT with the aid of tractography may be implemented in VIM targeting to place at least 1 contact within this white matter bundle that can be used later as a backup in the case of VIM habituation.

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**Disclosures**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**Author Contributions**

Conception and design: Remore, Rifi, Tsolaki, Bari. Acquisition of data: Remore, Rifi, Wei, Tolossa, Bari. Analysis and interpretation of data: Remore, Rifi, Bari. Drafting the article: Remore, Rifi, Tsolaki, Wei, Bari. Critically revising the article: Remore et al.
Rifi, Tsolaki, Ward, Locatelli. Reviewed submitted version of manuscript: Remore, Rifi, Tsolaki, Ward, Wei, Locatelli. Approved the final version of the manuscript on behalf of all authors: Remore. Statistical analysis: Remore. Study supervision: Tsolaki, Wei, Bari.

Supplemental Information
Previous Presentations
Some contents of this work were presented as a poster during the 1st Congress of the DBS Society, June 22–23, 2023, in Grenoble, France.

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