Anatomic Targeting of the Optimal Location for Thalamic Deep Brain Stimulation in Patients with Essential Tremor

Nicolas K.K. King[1,3], Vibhor Krishna[1,4], Francesco Sammartino[1], Ausaf Bari[1], Gaddum Duemani Reddy[1], Mojgan Hodaie[1], Suneil K. Kalia[1], Alfonso Fasano[2], Renato P. Munhoz[2], Andres M. Lozano[1], Clement Hamani[1]

BACKGROUND: **Thalamic deep brain stimulation (DBS) is an effective strategy for treatment of essential tremor (ET). With limitations of imaging modalities, targeting largely relies on indirect methods. This study was designed to determine the optimal target for DBS in ET and construct a targeting method based on probabilistic maps.**

METHODS: **Patients with ET who had sustained tremor reduction at 1 year and optimal microelectrode recordings were selected. Stimulation volume was individually modeled in standard space, and a final optimal region was derived for the whole population. A fornix (FX) targeting method was developed to determine the location of the optimal stimulation site relative to the FX and posterior commissure (PC) in the anteroposterior plane, the border between the thalamus and internal capsule in the mediolateral plane, and the anterior commissure (AC)–PC (AC-PC) plane in the dorsoventral axis. Following comparative analyses with other standard indirect methods (25% of AC-PC and PC + 6 mm), the FX method was studied in relation to diffusion tensor imaging.**

RESULTS: **Using the FX method, the optimal stimulation site was at the intersection of two thirds and one third of the PC-FX distance (mean of 28% ± 1.5 AC-PC length) and 4 mm medial to the lateral border of the thalamus. Compared with previously used methods, there was a significant reduction in variability of the optimal stimulation site with the FX method. The target defined using this strategy was found to be within the boundaries of the dentatorubrothalamic tract.**

CONCLUSIONS: **The FX method may be an additional targeting strategy in patients undergoing thalamic DBS surgery.**

INTRODUCTION

Long-term stimulation of the ventral intermediate nucleus (Vim) of the thalamus has been shown to be effective for the surgical treatment of medically refractory tremor.[1,2] The Vim as a target was initially selected for lesioning and subsequently for deep brain stimulation (DBS).[3] In this thalamic region, movement-related kinesthetic and tremor cells coexist,[4-6] rendering electrophysiology a main strategy for targeting the Vim.[2,7] Precisely targeting the Vim is crucial for long-term improvement of tremor. Previous studies have shown that even small deviations from the optimal location may result in a suboptimal outcome.[8,9]

As currently used in the clinic, structural magnetic resonance imaging (MRI) is not able to visualize thalamic nuclei, even with

Key words
- Deep brain stimulation
- Diffusion tensor imaging
- MRI
- Targeting
- Thalamus
- Tremor

Abbreviations and Acronyms
AC: Anterior commissure
ACPC25%: 25% of anterior commissure–posterior commissure
DBS: Deep brain stimulation
DRT: Dentatorubrothalamic tract
DTI: Diffusion tensor imaging
ET: Essential tremor
FX: Fornix
MRI: Magnetic resonance imaging
PC: Posterior commissure
PC+6: Posterior commissure + 6 mm
Vim: Ventral intermediate nucleus

From the [1]Division of Neurosurgery, Department of Surgery, and [2]Morton and Gloria Shulman Movement Disorders Clinic and Edmond J. Safra Program in Parkinson's Disease, Division of Neurology, Department of Medicine, University of Toronto, Toronto Western Hospital, Toronto, Ontario, Canada; [3]Department of Neurosurgery, National Neuroscience Institute, Singapore; and [4]Center for Neuromodulation, Department of Neurosurgery, The Ohio State University, Columbus, Ohio, USA

To whom correspondence should be addressed: Clement Hamani, M.D., Ph.D. [E-mail: c.hamani@utoronto.ca]
Citation: World Neurosurg. (2017) 107:168-174.
http://dx.doi.org/10.1016/j.wneu.2017.07.136

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

specialized sequences or diffusion imaging.[10-12] Commonly used approaches to target the Vim are based on formulaic methods that derive coordinates relative to the anterior commissure (AC) and posterior commissure (PC).[8,13,14] However, such approaches are insensitive to the variability of thalamic morphology and the size of the third ventricle. Both factors can contribute to errors in correctly identifying the Vim, which may ultimately lead to a suboptimal outcome. Our aim was to determine the optimal target for chronic DBS for essential tremor (ET) and construct an anatomic targeting method based on this probabilistic map to overcome the limitations in identifying thalamic subdivisions on MRI sequences.

MATERIALS AND METHODS

Study Population

The study was approved by the institutional review board of the University Health Network. Records of patients with ET treated with Vim DBS at Toronto Western Hospital within the last 5 years were reviewed. To develop our targeting-based system, we selected patients who met 3 inclusion criteria. First, patients needed to have disabling medically refractory ET, as determined by a movement disorders neurologist. Second, intraoperative microelectrode recording had to show the presence of kinesthetic cells and/or tremor cells as well as tremor arrest during microstimulation. Third, patients needed to have tremor reduction of at least 50% compared with baseline after optimization of stimulation parameters at 1 year of follow-up or longer, as measured with the Fahn-Tolosa-Marin Tremor Rating Scale.[15] These criteria were selected such that patients with good electrophysiology recordings and clinical outcomes were included in this study. Contacts with the best therapeutic window, maximal benefit, and least side effects were chosen during the programming for long-term Vim stimulation. In the patients selected, postoperative improvement was of 70% ± 17. For this initial part of the study, 10 patients (5 women) met the inclusion criteria. Of these patients, 7 underwent left unilateral procedures, and 3 subsequently had staged bilateral DBS. The left-sided electrode was analyzed in all cases yielding 10 DBS electrodes for analysis.

Surgical Technique

A Leksell G stereotactic frame (Elekta AB, Stockholm, Sweden) was applied using local anesthesia. MRI was performed using a 1.5T scanner (Signa Excite; GE Healthcare, Wauwatosa, Wisconsin, USA). Using FrameLink software (Medtronic, Minneapolis, Minnesota), coordinates of AC and PC were determined, and the images were reformatted parallel to the AC-PC plane and orthogonal to the midline. The selection of the first tract was based on the indirect target at the intercommissural line.

Details of microelectrode mapping and signal processing were previously described.[16] Briefly, extracellular single and multiunit activity was recorded. Tremor cells were identified based on the following criteria: isolated single thalamic units firing in bursts (5–10 in a train) that occurred at frequencies of 3–10 Hz and were synchronous to the patient's tremor. Kinesthetic cells were identified based on their responses to movement-related activity. Microstimulation (25–100 μA, 0.2-ms pulse width, 300 Hz, 1-second train) was used to test for contralateral tremor reduction or tremor arrest. Sites with tremor cells, kinesthetic cells, and tremor reduction or arrest during microstimulation were selected as targets for the insertion of DBS electrodes. In all patients, a quadripolar DBS electrode model 3387 was used combined with either a Soletra or an Activa SC pulse generator (Medtronic). The ring angle was 61° ± 7, and the arc angle was 103° ± 2.6.

Volume of Tissue Activation of Active Contact

A high-resolution T1-weighted spoiled gradient recalled MRI scan (repetition time/echo time = 12/5 ms, field of view = 260 mm, reconstructed voxel 0.5 × 0.5 × 0.7 mm^3) was acquired using a 1.5T scanner (Signa Excite) for each patient in the immediate postoperative period. For spatial normalization, structural images were registered to the Montreal Neurological Institute 152 template with a 12-parameter affine transformation and a nonlinear warping algorithm using Analysis of Functional NeuroImages software (http://afni.nimh.nih.gov/afni). The location of the active contact, defined here as the cathode, was determined in Montreal Neurological Institute 152 space. The volume of tissue activation surrounding the active contact was modeled using an ellipsoid based on a previously described method[17,18] and implemented in MATLAB (The MathWorks, Inc., Natick, Massachusetts, USA). The probability of each voxel being activated out of the whole cohort of volumes of tissue activated was calculated as an activation threshold. To be included in the final activated volume, a minimum activation threshold of 80% was selected. This volume was spline interpolated and mapped onto the Schaltenbrand and Wahren atlas.[19]

FX-Based Method and Comparison with Formulaic Methods

Based on the results of the optimal volume of activation (Figure 1), we constructed a fornix (FX)-based anatomic targeting method. Our aim was to develop a method that would account for the variability in the anteroposterior length of the thalamus and for the width of the third ventricle. This was then compared with 2 commonly used indirect formulaic methods. In the 25% of AC–PC (ACPC25%) method, the *y*-coordinate was anterior to PC by 25% of the AC-PC length, and the *x*-coordinate was 10 mm from the wall of the third ventricle.[8] In the PC + 6 mm (PC+6) method, the *y*-coordinate was 6 mm anterior to PC, and the *x*-coordinate was 15 mm from the midline.[14]

As shown in Figure 2, the *y*-coordinate in the FX method was first determined as one third of the distance measured from the posterior border of PC to the middle of the FX at the level of the AC-PC plane. The *x*-coordinate was determined as the point 4 mm medial from the lateral border of the thalamus also at the AC-PC plane. The intersection of these 2 points was considered to be the target for implanting the tip of the electrodes.

After all the analyses were complete, the optimal target location ascertained with each targeting strategy was converted to a region of interest mask and transformed back from Montreal Neurological Institute space into single subject space for each patient to identify the optimal location at the level of the intercommissural plane. This location was compared with locations obtained by the 3 targeting methods in the *x*-axis and *y*-axis. The radial error, the shortest distance between the optimal target and the target of the chosen targeting method in the axial plane, was also calculated.