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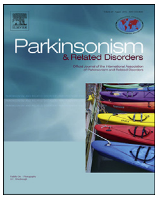

Precise stimulation location optimizes speech outcomes in essential tremor

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ABSTRACT

Background: Deep brain stimulation for essential arm tremor is often complicated by dysarthria and persistent voice tremor.
Objective: To determine the relationship of stimulation location to speech outcomes following bilateral thalamic deep brain stimulation (DBS) for essential tremor (ET).
Methods: Eighteen patients undergoing bilateral DBS for ET were prospectively studied. Speech pathologists grouped patients by final speech outcome (normal speech, voice tremor, or dysarthria). Locations of the active leads were calculated by normalizing the segmented thalamic volumes to those in the Morel atlas. Stimulation volumes within thalamic nuclei, error distances from target, and measures of accuracy were calculated and differences in measures between outcome groups tested.
Results: At optimal stimulation, 8 patients had normal speech, 6 had voice tremor, and 4 had mild dysarthria. Stimulation volumes were statistically concentrated within the ventral lateral posterior nucleus (VLp). The percentage of stimulation volume outside the VLp was higher in patients with dysarthria (60% vs. 24%, $p = 0.02$) or voice tremor (55% vs. 24%, $p = 0.03$) compared to patients with normal speech outcomes. The error distance from the center of VLp was greater for patients with dysarthria than those with normal speech (12.6 vs. 7.6 mm, $p = 0.02$). Electrodes with lower efficiency for VLp stimulation were more frequent with poor speech outcomes and in patients with persistent voice tremor.
Conclusions: Following bilateral DBS for ET, 22% of patients develop a non-disabling dysarthria. Optimal speech outcomes were achieved in 44% of patients and correlated with precise stimulation location within and not outside of the VLp.

1. Introduction

Thalamic deep brain stimulation (DBS) results in improvement of essential arm tremor in 92% of patients [1]. In the thalamotomy era, bilateral procedures carried the risk of severe speech impairment. Bilateral thalamic DBS though safer, nonetheless carries an estimated 38% risk of dysarthria [2,3]. Also, the success of DBS in the treatment of essential voice tremor is less predictable [4,5]. Thus, the remarkable success of DBS in alleviating disabling arm tremor in essential tremor (ET) contrasts with the unpredictability of attaining optimal speech outcome (defined as no voice tremor or dysarthria).

Optimizing speech outcomes requires a greater understanding of the principles that relate stimulation location to therapeutic and adverse speech effects. Towards that goal we prospectively studied eighteen patients treated with bilateral DBS for ET. Recently, structural-functional analysis in DBS has benefited from the calculation of the volume of tissue activated (VTA) by the stimulating lead and by the application of computerized digital atlases [6]. We applied the digital Morel atlas, a three-dimensional model of the human thalamus, to develop an individualized method for mapping stimulation volumes [7]. Using this method, we were able

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to identify several principles that could lead to improved speech outcomes with bilateral thalamic DBS.

2. Methods

Twenty consecutive patients undergoing bilateral thalamic DBS for intractable essential arm tremor between February 2007 and April 2009 enrolled in this protocol which was approved by the Mayo Clinic institutional review board. All patients provided written informed consent. Eighteen patients completed the entire protocol. Two patients did not complete the protocol (one did not have surgery; one did not have post-operative MRI).

Speech evaluations were performed and recorded pre- and post-operatively after optimal stimulator programming. Speech tasks included vowel prolongation, speech-like alternating and sequential motion rates, reading a standard passage, picture description, and a spontaneous language sample. Audio-recorded exams were scored independently by two speech pathologists (JD and ES) blinded to pre-versus post-operative status. Inter-rater reliability across judgments of tremor presence and severity, dysarthria presence and severity, and speech intelligibility was 92%. The clinical ratings were subsequently divided into three outcomes: 1) normal speech, 2) voice tremor, indicating tremor with prolonged vowels as an isolated abnormality (i.e., no other features of dysarthria) and 3) dysarthria, indicating impaired speech characteristics in addition to, or other than tremor [8]. Optimal stimulator programming occurred when patients achieved the best arm tremor control with minimal side effects. During programming at least one session included the testing of all monopolar electrode combinations at escalating voltages.

2.1. Surgery

All patients underwent same day bilateral thalamic DBS lead implantation. In all patients the Medtronics 3387 leads were used. A Medtronics Kinetra stimulator was implanted in 17 patients and two Medtronics Soletra stimulators were implanted in one patient. In all patients the ventro-intermedialis nucleus of the thalamus was targeted using COMPASS software. Surgery was performed awake using a Leksell frame system and microelectrode mapping. All patients had immediate post-operative MRI to assess electrode placement.

2.2. Mapping protocol

Mapping of electrodes was performed using the Morel 3D atlas applied to post-implantation MRIs [7]. Preoperative MRI images (MP-RAGE, 1 mm thick slices) were segmented using the FSL-FIRST algorithm to determine thalamic margins which were subsequently normalized to the thalamic margins of the MNI template. Postoperative images were co-registered to the preoperative images and subjected to the deformation field calculated above to bring the thalamic margins of the postoperative image into MNI space [9]. Electrode centers were then marked and recorded as MNI coordinates. In addition to the active clinical contacts, we mapped contacts that produced dysarthria with unilateral stimulation during threshold testing.

2.3. Measures

Electrode location, voltage, and therapy impedance at optimal stimulation were used to map the VTA. If stimulation was bipolar, the location was entered as the midpoint between the active electrodes. Spheres of stimulated volume were calculated using a published algorithm [10]. Using the digital Morel atlas, the VTA in cubic millimeters (mm^3) within the major thalamic nuclear groups and specific thalamic nuclei were calculated.

This mapping protocol was entirely independent of that used in the surgical planning software and formed an unbiased and more accurate analysis of electrode placement. We assessed if VTAs were significantly concentrated within specific thalamic nuclear groups and if so if VTAs further concentrated within specific thalamic nuclei within that group. Analysis also determined if there was an interaction between stimulation location and speech or arm tremor outcomes. Probability maps demonstrating the common areas of stimulation within groups were generated following a method previously reported [6].

As the surgery targeted the ventro-intermedius nucleus of the Schaltenbrand-Wahren atlas (Thieme, New York, NY), we analyzed the accuracy of stimulation within the VLp (the analogous nucleus in the Morel atlas) [11]. We calculated the VTA within VLp, VTA outside of VLp, and percent of VTA outside of VLp. The distance between the electrode location and geometric center of the VLp represented the error distance. We modeled the efficiency of electrode stimulation by plotting percent of VTA out of VLp for increasing radii of stimulation from 0.5 mm to 4 mm (corresponding to stimulation voltages of < 0.1–4 V at an impedance of 1000 Ω). Electrodes were classified as high efficiency (VLp-high, percent out $< 40\%$ at all radii), moderate efficiency (VLp-mid, percent out with values between 40 and 60%), and low efficiency (VLp-low, percent out $> 60\%$ at all radii).

2.4. Statistics

Two-factor ANOVA was used to test for the group concentration of VTA within given locations and for interaction between location and speech outcome and final arm tremor rating. Post-hoc analysis of significant effects was performed with Bonferroni analysis with $p < 0.05$. Unpaired two-tailed t-tests or chi-square analysis were used to compare stimulation accuracy measures between outcome groups. A p-value of <0.05 was considered significant.

3. Results

The 18 patients who completed the study had a mean age of 63.3 (range 55–84) years and 10 were female. (Table 1) Essential voice tremor was present in 12/18 (67%) patients pre-operatively. Optimal stimulation was reached at a mean of 51 days (range 15–108 days) after surgery. (Table 1) Patients with dysarthria had stimulation adjusted for 77–97 days before stimulation was declared optimal to exclude the additive effect of swelling after surgery. No patient had dysarthria with unilateral stimulation using an electrode configuration used at optimization. After DBS, speech outcomes were graded as normal in 8/18 (44%) and voice tremor in 6/18 (33%). Four patients (22%) had dysarthria characterized as mild to moderate with preserved intelligibility. Voice tremor persisted post-DBS in older patients compared with those with normal voice outcomes (mean 71.3 vs. 62.1 years; confidence interval, 1.0–17.4; $p = 0.03$).

Six contacts were found that produced dysarthria with unilateral stimulation (Supplementary Table 1). These contacts had a higher percentage of volume outside the thalamus than contacts used for optimal clinical stimulation (mean 38% vs. 4%; confidence interval 21.2–47.1%; $p = 4.5 \times 10^{-6}$) and appeared to have VTAs involving the internal capsule (Supplementary Fig. 2).

For the active contacts used for bilateral stimulation, VTAs demonstrated a wider spatial dispersion within the thalamus in persistent voice tremor or dysarthria outcomes than in normal voice outcomes (Fig. 1). For all patients, VTAs were significantly related to thalamic nuclear group [$F(2,7) = 17.3$, $p = 1 \times 10^{-15}$] with post-hoc analysis indicating a significant difference between the