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Dentate nucleus stimulation for essential tremor

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Thalamus ventral intermediate nucleus deep brain stimulation is a well-recognized therapy for refractory essential tremor (ET) [1]. However, cortical atrophy and microangiopathy may present a greater surgical risk especially in older patients. In this context, alternative targets for neuromodulation in ET may be relevant. Cerebellar neuromodulation has emerged with promising results in movement disorders [2]. Although there have been only a few studies, non-invasive and invasive stimulation over the cerebellum has been shown to potentially improve ataxia, dystonia, and tremor [2–5]. Here, we report the case of a patient with refractory ET who underwent dentate nucleus DBS (DN DBS).

A 76-year-old right-handed male presented with a 50-year history of tremor in uppers limbs and voice that became incapacitating over the last 20 years. He was diagnosed with essential tremor and had been taking 200 mg of primidone with initial improvement, but symptoms worsened over the last 5 years. Propranolol was not tolerated over 40 mg due to hypotension effect. By the time of his first visit he was not able to write, drink, or eat because of the high amplitude tremor (Motor part of Fahn, Tolosa, Marin Tremor Scale = 65/120). Considering the refractoriness of his symptoms and severity of the tremor he was referred to DBS surgery. However, because of his marked brain atrophy and leukoencephalopathy, considering the higher risks of bleeding, the dentate nucleus was proposed as a target. The study was approved by the local ethics committee and the patient provided written informed consent.

The surgical procedure was described elsewhere [3] and is detailed in supplementary file 1. Fig. 1 illustrates the target. The DBS was turned on one month after surgery. During the follow-up, we tested a range of frequencies between 6 and 150 Hz and pulse widths between 60 and 210 μ s. We tested each electrode separately and then both sides together, first using monopolar and after using bipolar settings. The tremor improvement was seen ipsilateral to the stimulated lead when tested unilaterally. The patient was assessed every 28 days and parameters were changed in all visits according to tendencies, patient's improvement, or collateral effects. Once the best parameters were defined, nine months after surgery, the configuration was kept constant until the double-blind evaluation, at the one-year follow-up. During the double-blind evaluation, the patient was assessed under off- and on-stimulation conditions. Both conditions were introduced 30 min before the clinical ratings in randomized order, with both patient and evaluator blinded to the DBS status. The best settings were bipolar and

activated the most proximal contacts (left DN = 1.6 mA, 78 μ s, 138 Hz; right DN = 1.2 mA, 117 μ s, 138 Hz).

We observed an improvement in tremor with a 48% reduction in Motor part of Fahn, Tolosa, Marin Tremor Scale (from 66/120 to 34/120) and a 71% reduction in tremor amplitude using the Weber-Fechner Relationship when comparing the active versus sham phases. Part of this evaluation can be seen at the supplementary video. Dizziness was noted with a higher pulse width on monopolar stimulation and some habituation could be seen over the months. Patients' global impression of change (PGIC scale) during the last follow-up was 6 (better, and definitive improvement that has made a real difference).

In this pilot case, DN DBS in a patient with ET was a safe and well-tolerated procedure with no major side effects during the 12-month follow-up period. The effect on tremor was remarkable in the blinded assessment one year after the surgery. Additionally, the stimulation significantly improved his functionally, including the handwriting (from 4 to 2 points in item 10 of Fahn, Tolosa, Marin Tremor Scale).

Thus far, clinical studies have only evaluated the effects of DN DBS in single cases. Although only small improvements were noted, DN DBS was effective for treating ataxia in SCA type 3 [3], cerebellar stroke [4], and dystonia [5]. To our knowledge, this is the first report for ET. Treatment involving DBS of the VIM and posterior subthalamic area targeting the fibers of the dentatothalamic tract (DTT) has been shown to be effective for treating ET. We postulate that DN stimulation can be effective in reducing tremor by modulating the nucleus excitatory activity and targeting the DTT at its origin. Larger studies are necessary to address whether DN DBS is in fact effective over short- and long-term periods for ET and to better determine the optimal site of electrode placement and parameters for stimulation.

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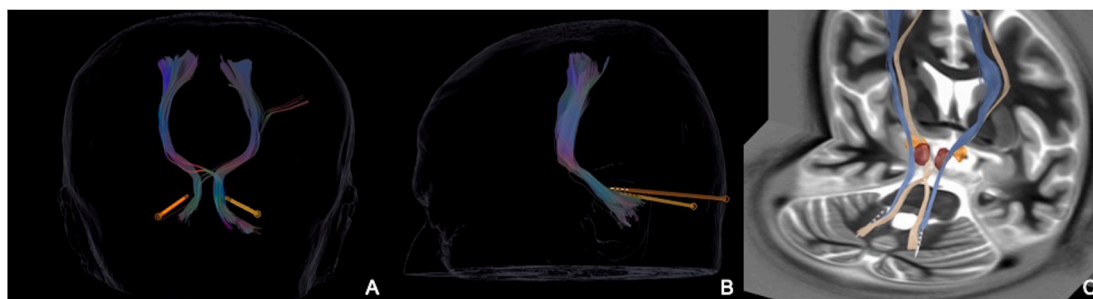


Fig. 1. Bilateral deep brain stimulation (DBS) of the dentate nucleus and relation with dentatorubrothalamic tracts (DRTT). Three-dimensional depictions of electrode placement in the dentate nucleus and its relations to the dentate-rubro-thalamic tract (DRTT). Fig. 1A and B result from a co-registration of pre-operative MRI with patient-specific deterministic tractography and post-operative CT (Elements Software, Brainlab AG, Germany). Fig. 1C originates from a co-registration of pre-operative MRI and post-operative CT, however normalized to the MNI space and comparing electrode position with a normalized DRTT projection (LEAD DBS Software, Horn & Kuehn, Germany).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.parkreldis.2020.12.001>.

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