



Technical Notes

# Dentate nucleus deep brain stimulation: Technical note of a novel methodology assisted by tractography

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## ABSTRACT

**Background:** The cerebellum has emerged as an attractive and promising target for neuromodulation in movement disorders due to its vast connection with important cortical and subcortical areas. Here, we describe a novel technique of deep brain stimulation (DBS) of the dentate nucleus (DN) aided by tractography.

**Methods:** Since 2015, patients with movement disorders including dystonia, ataxia, and tremor have been treated with DN DBS. The cerebellar target was initially localized using coordinates measured from the fastigial point. The target was adjusted with direct visualization of the DN in the susceptibility-weighted imaging and T2 sequences of the MRI and finally refined based on the reconstruction of the dentatorubrothalamic tract (DRTT).

**Results:** Three patients were treated with this technique. The final target was located in the anterior portion of DN in close proximity to the DRTT, with the tip of the lead on the white matter and the remaining contacts on the DN. Clinical outcomes were variable and overall positive, with no major side effect.

**Conclusion:** Targeting the DN based on tractography of the DRTT seems to be feasible and safe. Larger studies will be necessary to support our preliminary findings.

**Keywords:** Deep brain stimulation, Dentate nucleus, Dentatorubrothalamic tract, Tractography

## INTRODUCTION

A key anatomical feature of the cerebellum is the deep cerebellar nuclei.<sup>[2,3]</sup> Among these, the dentate nucleus (DN) is the largest, located within the cerebellar white matter adjacent to the fourth ventricle roof, and related to functions of planning, initiating, controlling volitional movements, and cognition.<sup>[2,3,27,32,37]</sup>

The DN has connections with different cortical and subcortical areas, making it a strategic target.<sup>[3]</sup> It receives afferent fibers from the premotor cortex, supplementary motor cortex, and also from the spinocerebellar tract. Its largest efferent is the dentatorubrothalamic tract (DRT) fiber bundle that plays a role not only in motor functions but also in cognition and behavior.<sup>[15,17,19,37]</sup>

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The use of the DN as a target for the treatment of different movement disorders dates back to 1935, when Delmas-Marsalet and Von Bogaert performed the first ablation of the DN in a Parkinsonian patient.<sup>[12]</sup> At the beginning of the 1970s, Irving Cooper started implanting surface electrodes to stimulate the cortex of the anterior lobe of the cerebellum for cerebral palsy.<sup>[8]</sup> Ablative lesions and stimulation of the DN were performed in the treatment of different pathologies overtime.<sup>[16,22,36,38]</sup>

Recently, cerebellar modulation has reemerged as a promising therapy in the movement disorders field. Noninvasive stimulation of the DN showed encouraging results. Despite this, there are few centers with experience in deep brain stimulation (DBS) of this target and its effect has been evaluated only in single cases. Thus far, small improvements were noted, DN DBS was effective for treating ataxia in SCA type 3, cerebellar stroke, dystonia, and essential tremor.<sup>[5,9,10,18,25,35]</sup>

References in the literature to electrode placement in DN use atlas coordinates rather than direct MRI visualization, probably a result of the difficulty of seeing the DN on conventional imaging. This fact may have limited the interest for the target.<sup>[13,23]</sup>

With the evolution of technique and image quality, the ability to identify the DN has improved.<sup>[13,20,23]</sup> In addition, tractography has gained a prominent role since it has been suggested that stimulation of white matter pathways near targeted structures may contribute to therapeutic effects of DBS.<sup>[6,29]</sup>

In this paper, we detailed for the 1<sup>st</sup> time the surgical technique used by our group to perform DN DBS based on specific MRI sequences associated with tractography of the dentatorubrothalamic tract (DRTT).

## METHODS

Between July 2015 and September 2020, three patients with refractory movement disorders including tremor, dystonia, ataxia, and stroke were treated with unilateral or bilateral DN DBS at the University of São Paulo, Brazil. Data were obtained from patients included in a research protocol approved by the ethics committee of the mentioned institution. Epidemiological characteristics and etiological diagnosis are summarized in [Table 1].

Before surgery, contrast-enhanced volumetric T1, T2, susceptibility-weighted imaging (SWI), and fluid-attenuated inversion recovery, MRI scans were obtained in axial sections with a 1.5 T Siemens Espree scanner (Siemens, Munich, Germany). Diffusion tensor imaging (DTI) was acquired with the following specifications: single-shot, 2-dimensional; echo-planar imaging; repetition time (TR), 6700 ms; echo time (TE), 95 ms; diffusion values, b=0 s/mm<sup>2</sup> and

**Table 1:** Summary of dentate nucleus DBS published by this group.

DN DBS	Number of cases	Gender	Age (years)	Diagnose	Symptoms	FTMRS		SARA		DBS	DBS settings	Adverse events
						Baseline	Active DBS	Baseline	Active DBS			
Teixeira <i>et al.</i> , 2015 <sup>[36]</sup>	Single case	Female	50	Cerebellar stroke	Ataxia, dystonia, tremor	38	24	25.5	17	Unilateral	Bipolar –Most proximal contacts 1.4 mA 60 µs 20 Hz	None
Cury <i>et al.</i> , 2019 <sup>[10]</sup>	Single case	Female	31	Spino-cerebellar ataxia-3	Ataxia	23	16	15.5	12	Bilateral	Bipolar –Most dorsal contacts Left 2.0 mA 182 µs 16 Hz Right 1.8 mA 182 µs 16 Hz	None
Paraguay <i>et al.</i> , 2020 <sup>[25]</sup>	Single case	Male	76	Essential tremor	Tremor	66*	34*	-	-	Bilateral	Bipolar –Most proximal contacts Left 1.6 mA 78 µs 138 Hz Right 1.2 mA 117 µs 138 Hz	None

\*Motor part of FTMRS. FTMRS: Fahn, Tolosa, and Marin Tremor Scale, SARA: Scale for the assessment and rating of ataxia

$b=1000$  s  $\text{mm}^2$ ; diffusion directions, 20; slice count, 50; voxel size,  $2.6 \times 2.6 \times 2.7$   $\text{mm}^3$ ; and acquisition time, 9:07 min.

On the day of surgery, a stereotactic frame (Aimssystem, Micromar, Brazil) was placed on the patient's head under local anesthesia and stereotactic contrast-enhanced computed tomography scan was performed.

Registration of image sets and target planning was subsequently performed using the MNPS Software (MEVIS neurosurgery planning system, MEVIS, Brazil) and deterministic tractography was performed using DSI studio software ([www.dsi-studio.labsolver.org](http://www.dsi-studio.labsolver.org)). DRTT fiber bundle was reconstructed using a region of interest (ROI) in the DN and another in the red nucleus (RN). The regions of interest were selected manually, atlas was used for confirmation. The definition of the ROI was made by two surgeons.

Tractography, based on diffusion-weighted imaging (DWI), is a technique with great potential to characterize the *in vivo* anatomical position and integrity of white matter tracts (Basser *et al.*, 2000; Behrens *et al.*, 2003; Mori *et al.*, 1999). Tractography has proven its worth in neuroscience as well as in neurology and neurosurgery (Bick *et al.*, 2012; Dimou *et al.*, 2013; Potgieser *et al.*, 2014). It is an invaluable tool in investigating structure–function relationship.

### Target planning

Coordinates described by Weigel *et al.*<sup>[38]</sup> were used and target points were located as follows: 5 mm posterior, 10 mm inferior to the fastigial point, and 14 mm lateral to the midline. Depending on the diagnose, the procedure was performed unilaterally or bilaterally.

The target position was then adjusted using direct visualization of the DN in the SWI and T2 sequences previously to coregistration to stereotomography and T1 contrast-enhanced volumetric MRI. The target was refined to be located in the anterior and upper third of the DN, region related to motor function.

In the next step, adjustment was performed to keep the target within the DN, being as close and parallel as possible to the DRTT fibers [Figure 1a-c].

The entry points were planned to provide a safe trajectory through suboccipital bone, avoiding proximity to the venous sinuses and vessels visualized on the contrasted images.

### Procedure

After planning the trajectory, the patients underwent a surgical procedure to implant the cerebellar electrodes. All cases were operated under general anesthesia and were positioned in prone with the skull fixed in flexion to facilitate access to the posterior fossa [Figure 2a].

Straight incisions of 3–4 cm in the suboccipital region were performed based on the stereotactic coordinates of the entry points [Figure 2b]. Burr holes were drilled and microelectrode recording (MER) was done before electrode implantation [Figure 2c].

Microelectrodes of 130 mm length, 0.5 mm diameter, and 2 mm uninsulated recording tips were used (Inomed, Emmendingen, Germany). The record started 10 mm before the target and was performed up to 3 mm beyond the planned target point. The DN was identified on the MER by a region with intense electrical activity and continuous bursts of big spikes.<sup>[30]</sup> The spikes pattern or frequency was not altered by passive limbs movement. After 3–4 mm of DN MER, the electrode entered in white matter of the DRTT characterized by a region with no regular electrical activity, very few spikes, and a thin registry baseline [Figure 3a].

Quadripolar leads with 1.5 mm active contacts, 3 mm active tip, and 1.5 spacing (model 6145, Abbott, Memphis, USA) were implanted on the planned targets adjusted by the MER findings, ensuring the tip of the lead is located on the white matter and the remaining contacts on the DN. The electrodes location was confirmed intraoperatively with X-rays and then fixed in place with cyanoacrylate glue [Figure 3b and c].

In a subsequent procedure, the frame was removed, the patient was repositioned in supine position, electrodes were internalized and connected to a programmable implantable pulse generator (Libra XP, Abbott, Memphis, USA). The electrodes remained turned off after the procedure. Determination of optimal stimulation parameters for each electrode was based on a detailed test – stimulation protocol implemented on the postoperative follow-up.

Accurate lead placement was confirmed with a postoperative CT scan registered to preoperative target planning using Elements Software (Brainlab AG, Germany) [Figure 4a-c].

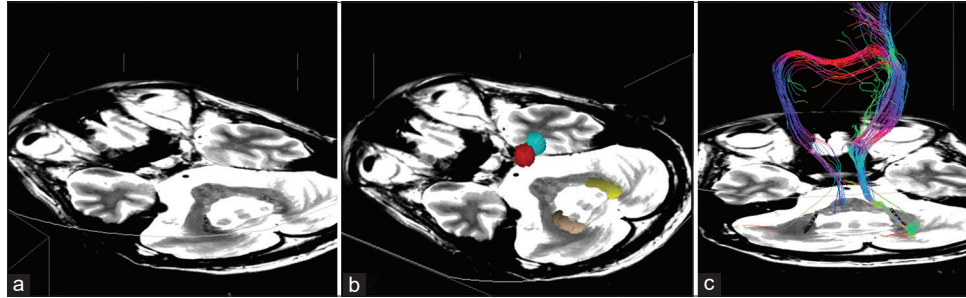
### Clinical outcomes

The clinical outcomes from the cohort have been published elsewhere<sup>[9,10,25,35]</sup> and data are summarized in [Table 1]. Overall, patients exhibited modest motor improvement in ataxia and tremor in blinded evaluations. No severe or permanent adverse events were noted. The procedure was well tolerated in all cases.

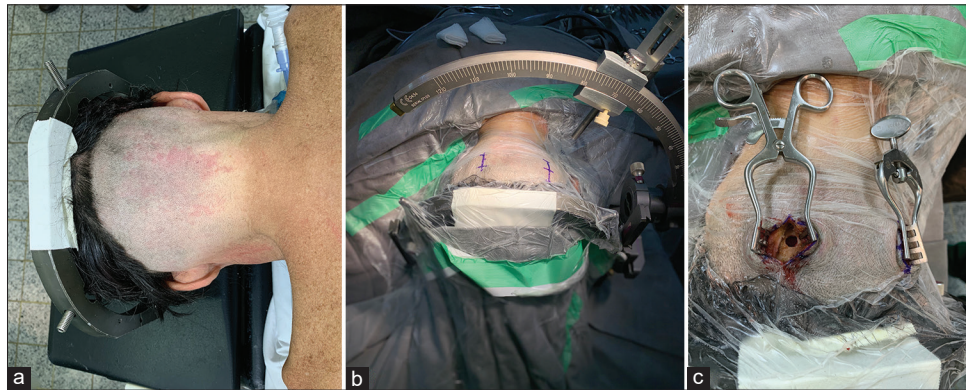
### DISCUSSION

DBS is a neurosurgical technique well established to treat different disorders.<sup>[17,29]</sup> With the better understanding about neurobiology, biomarkers, and progress in the quality of imaging, the potential uses of invasive neuromodulation and the number of anatomical targets have expanded.<sup>[37]</sup>

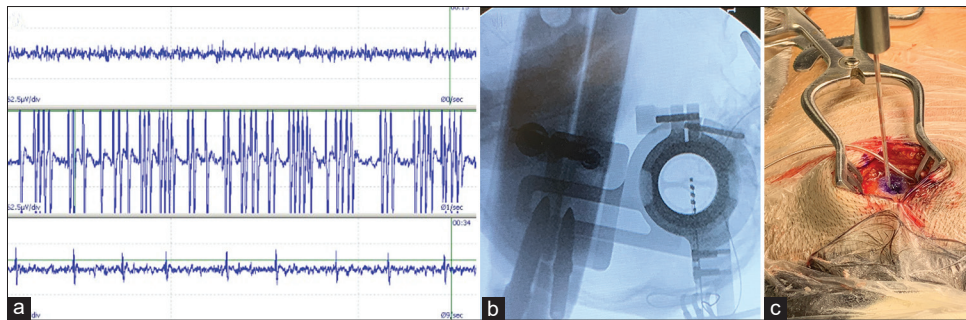




**Figure 1:** Planning target. (a) Axial T2 MRI showing bilateral dentate nucleus with electrodes position simulated. (b) Axial T2 MRI with regions of interest in dentate nucleus (brown and yellow volumes) and VIM (red and blue volumes). (c) Axial T2 MRI showing the planned position of the electrodes in the dentate nucleus and the relation with DRTT in the left side.



**Figure 2:** (a) Patient with frame positioned in prone, with the head flexed to expose the suboccipital region. (b) Bilateral straight incisions defined by stereotaxic coordinates. (c) Bilateral suboccipital burr holes.

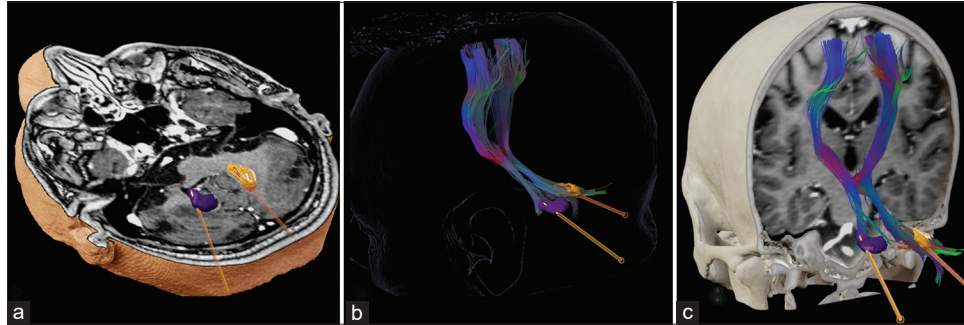


**Figure 3:** (a) Dentate nucleus microelectrode recording evidencing intense electrical activity. (b) X-ray confirming adequate electrode position intraoperatively. (c) Electrodes fixed in place with cyanoacrylate glue. (d) Bilateral suboccipital burr holes.

The DN is the largest of the deep cerebellar nuclei and plays a critical role in movement, cognition, autonomic functions, and behavior.<sup>[3,14,15,17,19]</sup> It is situated adjacent to the fourth ventricle buried by white matter and measures approximately 9–20 mm in width, 13–23 mm in length, and 7–20 mm in height. It has unique shape and is oriented in craniocaudal direction and from lateral to medial.<sup>[2,16,23]</sup> Functionally, the DN is divided into a dorsal motor domain and a ventral nonmotor domain that projects to diverse cortical areas.<sup>[37]</sup>

The use of the DN as target to treat movement disorders is not new. In 1935, Delmas-Marsalet performed the first surgical

procedure on the DN in humans to treat a patient with Parkinson's disease.<sup>[12]</sup> In 1961, Toth reported the results of dentatotomies in three Parkinsonian cases. Since then, several reports have been published about the benefits of dentatotomy in dystonia, choreoathetosis, and spasticity.<sup>[23,36]</sup> In 1972, Knutsson and Meyerson stimulated the DN for the treatment of spasticity and also confirmed somatotopic organization of the DN, with the head represented medially and the lower limbs laterally.<sup>[23]</sup> However, with the development of clinical treatments with baclofen and botulinum toxin and the rise of new targets, the use of DN was neglected for years.<sup>[23]</sup>



**Figure 4:** Postoperative image control. (a) Axial T1 gadolinium-weighted MRI reconstruction showing the adequate position of the electrodes in the dentate nucleus. (b) Three-dimensional reconstruction of DBS electrodes in bilateral dentate nucleus (purple and orange volumes) showing close relationship with DRTT (c) Coronal T1 gadolinium-weighted MRI reconstruction to evidence the bilateral electrodes, dentate nucleus, and DRTT. The 3D reconstructions and tractography were performed with Elements Software (Brainlab AG, Germany).

Recently, cerebellar modulation has reemerged as a promising therapy, in the field of movement disorders.<sup>[25]</sup>

The DN has connections with different cortical and subcortical areas, making it a strategic target. It receives afferent fibers from the premotor cortex, supplementary motor cortex, and also from the spinocerebellar tract.<sup>[2]</sup> Its major efferent is the DRTT that plays a role not only in motor functions but also in cognition such as planning, verbal fluency, working memory, abstract thinking, and behavior.<sup>[2,19,21,31]</sup> Connections between the DN and oculomotor, prefrontal, and posterior parietal regions of the cerebral cortex have been demonstrated.

Even with the current recognition of the role of the DN in movement disorders, studies evaluating the effects of cerebellar modulation are still rare. Horisawa *et al.*<sup>[18]</sup> described a case of a patient with fixed dystonia refractory to bilateral pallidotomy and intrathecal baclofen therapy that evolved with significant clinical improvement with DBS through the upper bilateral cerebellar peduncle and DN. Machado *et al.*<sup>[37]</sup> described motor recovery with stimulation of DN in rats with cortical stroke. Brown *et al.* reported a case of a 37-year-old female with severe dystonia that improved significantly after bilateral DN DBS.<sup>[4]</sup> Cury *et al.*<sup>[9]</sup> published the first long-term follow-up of a patient with a cerebellar stroke that improved tremor and ataxia after DBS of DN. Paraguay *et al.*<sup>[25]</sup> recently reported a case of a 76-year-old male with refractory essential tremor treated with the same procedure. Nicholson *et al.*<sup>[23]</sup> reviewed the neuromodulation of the DN in dyskinetic-dystonic syndromes.

The rationale related to the modulation of DN and DRTT is based in the fact that cerebellar lesions in some cases may decrease intracortical inhibition in the contralateral motor cortex, culminating in interhemispheric asymmetry of the cortical excitability, which could contribute to the motor impairment. Modulating the healthy DN and DRTT could increase contralateral intracortical facilitation, restoring cortical excitability symmetry.<sup>[9,10,11,34]</sup>

In the cases of ischemic cortical stroke, deafferentation and reduced activity of the cerebellum would happen, resulting in decreased excitatory output from the cerebellum to the affected cortex through the reciprocal dentatothalamocortical pathway. This phenomenon is a critical component of the rationale underlying the selection of the DRTT at the DN as a target.<sup>[37]</sup>

Our group has been one of the few to use DN to treat different pathologies. One of the limitations for targeting the DN is the difficulty for its proper identification using conventional imaging techniques. References in the literature to electrode placement describe the use of atlas coordinates rather than direct MRI targeting and it could lead to inaccurate electrode placement. Although the DN is properly seen on SWI, the field distortion limits its use. We chose to merge volumetric images of T1 and T2, as well as T2 and SWI, aiming targeting based on the direct visualization of the DN.

Despite the possibility of adjusting the stimulation with DBS in relation to dentatotomy, another critical point of the procedure is to achieve adequate location of the contacts in relation to the DN. In our surgical technique, we aim at the dorsal and medial anterior region of the DN that appears to be more related to motor function. Brown *et al.*<sup>[4]</sup> targeted the tip of each lead to the origin of the superior cerebellar peduncle (SCP) and Horisawa *et al.*<sup>[18]</sup> performed DBS through the bilateral SCP and DN.

The DRTT is a bundle that originates from the DN, runs in the SCP, and then mainly decussates to the contralateral RN to ascend to the thalamus and finally to the cortex.<sup>[5,19,26]</sup> In all cases, we obtained the tractography of the DRTT bilaterally and we aimed for the contacts to be close or within the projection of DRTT.

It is accepted that DBS can have influence over widespread areas of the brain, which have implications beyond the inhibition of a local gray matter structure. One of the mechanisms of DBS is to modulate circuit activity and fiber pathways in the vicinity of the electrodes. Considering this,

the use of tractography during targeting has been advocated in some applications of this technique.<sup>[6,28,29,33]</sup>

King *et al.*<sup>[29]</sup> reviewed 35 studies where the use of DTI in DBS was evaluated and concluded that the use of DTI for surgical planning is feasible, provides additional information over conventional targeting methods, and can improve surgical outcome. Patients in whom the DBS electrodes were within the DTI targets experienced better outcomes than those in whom the electrodes were not.<sup>[29]</sup> Coenen *et al.*<sup>[7,24]</sup> reported a tendency of clinically effective active contacts to be located closer to the modeled DRTT than the less effective active contacts. Abdalbaki *et al.*<sup>[11]</sup> observed that better tremor control in PD patients correlated with the distance of active electrode contacts to the DRT and suggested that tractography may optimize DBS targeting and postoperative adjustment of stimulation parameters.

In this paper, we systematically describe the technique used to target the DN assisted by tractography. The authors are not aware of the use of a similar technique. As limitations of this work, we have the restricted number of cases, the use of DTI with 50 slices and deterministic tractography. A detailed discussion about the merits and limitations of tractography is beyond the scope of this paper. Besides, the best target into the cerebellum DN or the DRTT or both has yet to be defined. Larger studies will be necessary to support our preliminary findings.

## CONCLUSION

The interest in the neuromodulation of the DN for the treatment of movement disorders has reemerged with better knowledge of its multiple connections with cortical and subcortical areas. Besides that, novel data have suggested that much of the benefit achieved from DBS is due to indirect stimulation of white matter pathways in close proximity to the active contact of the stimulating electrode. Considering this, we presented a feasible methodology to targeting the DN using the direct visualization with the help of specific sequences of MRI and based on the relationship with the DRTT.

## Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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