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Letter to the Editor

Neuronavigation-guided transcranial magnetic stimulation of the dentate nucleus improves cerebellar ataxia: A sham-controlled, double-blind n = 1 study

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Lesions of the cerebellum can lead to hypotonia, ataxia, intention tremor, and dystonia [1], which can be disabling and resistant to conventional treatments. The cererocerebellum receives input exclusively from the cerebral cortex (via pontine nuclei) and projects to the motor, premotor, and prefrontal cortices and to the ventrolateral nucleus of the thalamus via the dentate nucleus. It is involved in motor planning, motor learning, and fine-tuning of the motor activity, mainly by evaluating disparities between intention and action during the execution of movement. Cerebellar projections modulate activity in the contralateral primary motor cortex (M1) through dentothalamocortical projections. Acute ischemic damage to the deep cerebellar nuclei is known to result in ataxia and loss of excitatory input to the contralateral M1 cortex [1]. However, chronic cerebellar ischemic lesions have recently been associated with reemerging increase in intracortical inhibition in the contralesional M1, leading to marked inter-hemispheric asymmetry in cortical excitability, which could account for part of the functional impairment seen after stroke [2].

We report a case of post-surgical unilateral cerebellar infarction leading to dystonia, intention tremor, and ataxia treated by inhibitory low-frequency neuronavigated repetitive transcranial magnetic stimulation (rTMS) to the healthy cerebellar hemisphere. The aim was to decrease the functional cortical asymmetry related to chronic cerebellar infarction [2]. We hypothesized that this treatment would balance the functional asymmetry seen between both M1 after chronic cerebellar and attenuate clinical symptoms.

A 50-year-old female underwent a resection of a right acoustic neuroma in 2006, which was complicated by ischemia of the right cerebellar hemisphere (Fig. 1A). She developed severe axial and appendicular ataxia, mostly on the right, with significant impairment in functioning. A few months later, she developed bilateral involuntary hand and cervical dystonia (documented by electromyographic study), which was refractory to medical treatment. Several treatments were attempted for the cerebellar tremor, including: physical therapy, benzodiazepines, biperidene, beta-adrenergic blocking agents, and primidone, without

satisfactory symptomatic improvement. The patient declined deep brain stimulation for symptomatic tremor control. Because of the refractory nature of the symptoms, the subject consented to neuronavigated low-frequency TMS to the healthy dentate nucleus. A double-blind sham-controlled trial of 1 Hz neuronavigated rTMS was performed on the left dentate nucleus with a refrigerated double-cone rTMS coil (cooled DB-80, Magventure® Tonika-Elektronik, Denmark), which allows for the stimulation of deep structures up to 4–5 cm from the coil center. The dentate nucleus lay 50 mm deep from the skull surface, a distance similar to that of the skull vertex to the leg area at M1 (48 mm) (Fig. 1B). We detected the “hot spot” for M1 distal leg representation (peroneus longus muscle), and then its rest motor threshold was measured. The left dentate nucleus was then targeted by neuronavigation and a 1500-pulse session of either active or sham stimulation was performed at 90% of the rest motor threshold of the leg M1 area.

Two (active or sham) stimulation sessions were randomly performed four weeks apart. Clinical assessment and video recording were performed using validated tools before stimulation and one week after by movement disorder specialist blinded to the study. After the active session, there was improvement in tremor (Fahn, Tolosa, Marin Tremor Rating Scale before = 38/144; after = 24/144 37% reduction) and in cerebellar ataxia (scale for the assessment and rating of ataxia [SARA] before = 25.5/40, after = 17/40) (see video). The Patient Global Impression of Change (measured on a seven-point Leikert scale ranging from 1 to 7) was 6 after the active session (i.e. moderately improved) and 3 after the sham procedure (i.e. no change). There was no change in her dystonia after active treatment (Unified Dystonia Rating Scale = 9/112 before, and 9/112 after active stimulation). There was no clinical improvement after sham stimulations using the same rating scales **Table 1**.

Supplementary data related to this article can be found online at <http://dx.doi.org/10.1016/j.parkreldis.2015.05.010>.

The dentate nucleus has a tonic facilitatory influence on the motor cortex and controls multi-joint movements [3]. In primates, deep cerebellar nuclei have a primarily facilitatory effect on excitability in the contralateral primary motor cortex [1]. In rats, hemi-cerebellectomy decreases intracortical facilitation and blocks the facilitatory effects of somatosensory stimulation on M1 excitability [4]. In humans, TMS or electrical stimulation of the cerebellum given 5–7 ms before a TMS pulse is administered to the contralateral M1 results in M1 inhibition, which is reflected in decreased MEP amplitudes [3]. This is either due to preferential excitation of Purkinje cells, which inhibit the dentate nucleus, or to a direct disruptive effect of the TMS pulse upon output axons

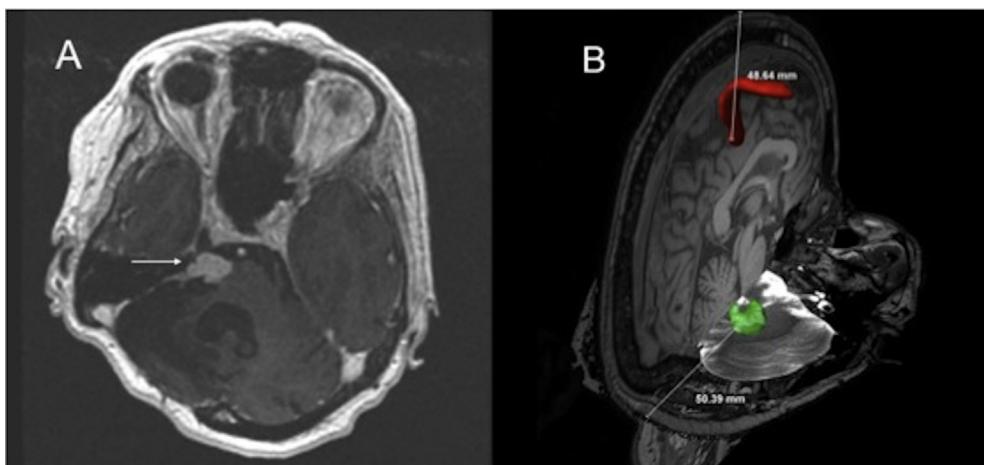


Fig. 1. Brain MRI. (A) Axial T1-weighted image showing cerebellar infarction in the right hemisphere and a partially resected right acoustic neuroma (arrow). (B) Sagittal FLAIR reconstruction of the dentate nucleus and the leg area at M1, showing a similar distance of both areas from the skull surface.

Table 1

Evaluation of dystonia, tremor and ataxia after active and sham rTMS of the dentate nucleus.

	Active rTMS		Sham rTMS		%change ^a
	Before	After	Before	After	
UDRS	09/112	09/112	09/112	09/112	none
SARA	25,5/40	17/40	25,5/40	25,5/40	33%
FTMTRS	38/144	24/144	38/144	38/144	37%

UDRS: Unified Dystonia Rating Scale; SARA: Scale for the assessment and rating of ataxia; FTMTRS: Fahn, Tolosa, Marin Tremor Rating Scale.

^a %change after Active rTMS.

exiting the cerebellum via the dentate nucleus. In fact, cerebellar infarctions result in acutely increased contralateral inhibition of M1, which probably reflects the increase in M1 intracortical inhibition related to the loss of dentate-cortical facilitatory projections. Consequently, there is a documented reduction in blood flow in the healthy cerebral hemisphere in cases of unilateral cerebellar infarction (crossed hemispheric diaschisis) [5]. However, chronic infarctions have been associated with decreased intracortical inhibition in the contralateral M1 [2], leading to an abnormal asymmetry in cortical excitability between both cerebral hemispheres. Based on these findings, low-frequency TMS has been employed to decrease (or inhibit) the activity of neurons in the remaining overactive cerebellar hemisphere, which would simulate the effects of dentatotomy on spasticity and dystonia.

This study has some limitations. It is difficult to produce an effective sham condition using TMS, especially using crossover designs. Although for the sham procedure the double-cone coil created noise and bumps similar to an actual coil, there was a lack of electric sensation in the scalp. Despite this drawback, this same approach has been used in numerous studies in the rTMS literature, providing results analogous to those using specific sham coils [6,7]. Another point that has to be considered is that while we ensured that the pulses reached the actual depth of the dentate nucleus by obtaining MEP's of the distal leg area in M1 and showing the similar depth between both targets, other areas of brain tissue were concomitantly stimulated with a less focused and less intense induced electric current. The presence of these "side-stimulations" is intrinsic to the rTMS method and its clinical role can only be assessed in future specific studies.

This was the first controlled, neuronavigation-guided deep-

rTMS study aiming at ataxia and tremor control. Despite limitations of sham rTMS, especially in crossover designs, and the fact that off-target cerebellar parenchyma was certainly stimulated due to inherent properties of rTMS coils, we obtained positive results. In our patient, the clinical improvement after active rTMS lasted for about 10 days and peaked from the sixth to the seventh day before gradually fading away. The reasons for these long-lasting effects remain uncertain. The study protocol was safe and well tolerated, and it provides sham-controlled evidence for larger studies using repetitive sessions of deep rTMS in this patient population.

Conflict of interest

The authors report no conflicts of interest or financial disclosures.

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