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1 **Dentate nucleus stimulation in a patient with cerebellar ataxia and tremor after**
2 **cerebellar stroke: a long-term follow-up**

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20 **Conflict of Interest**

21 The authors report no conflict of interest involved in this article.

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1 Cerebellar modulation has emerged as a promise therapy in the movement
2 disorders field, as cerebellum pathways present connections with critical cortical areas.
3 We have previously reported the short-term outcome in a patient with unilateral
4 cerebellar stroke who improved the ataxia after cerebellar neuromodulation [1,2]. The
5 rational hypothesis lies on the fact that unilateral chronic cerebellar ischemic lesions
6 were linked with a decrease in intracortical inhibition in the contralateral motor cortex,
7 culminating to inter-hemispheric asymmetry in cortical excitability, which could
8 contribute to the motor impairment [3]. Then, modulating the healthy dentate nucleus
9 could increase contralateral intracortical facilitation, restoring cortical excitability
10 symmetry (figure) [2]. We report here the 4-year results of this patient using a single-
11 blinded evaluation.

12 A 53-year-old female patient underwent a resection of acoustic neuroma,
13 complicated by stroke of the right cerebellar hemisphere. Due to the refractoriness of
14 her ataxia, we conducted double-blind trial of 1 Hz, transcranial magnetic stimulation
15 (TMS) to the left (“healthy”) dentate nucleus (DN). Based on her clear response to
16 TMS, after consent of the patient, she underwent DBS of the left DN. A double-blind
17 assessment 12 months after surgery showed tremor improvement by 37% and ataxia by
18 33%. Motor cortex excitability showed restoration of the asymmetry between both
19 hemispheres during on-condition (supplementary file 1). Details about the procedure
20 have been described [1,2].

21 Four years after surgery, the patient (unaware to DBS status) was assessed during
22 on-stimulation (1.9 mA, 60 μ s, 20 Hz) and 30 minutes after the DBS has been switched
23 off. The tremor continued to further improve (Fahn, Tolosa, Marin Tremor Rating Scale
24 [FTMRS] baseline=38, after=19/144 [50% reduction]) and the ataxia improvement
25 stabilized (scale for the assessment and rating of ataxia [SARA] baseline=25,

1 after=17/40 [33% reduction]) in the on-stimulation (video, supplementary file 2). When
2 the DBS was switched off, the patient spontaneously reported worsening the symptoms,
3 and the SARA worsened to 30/40 (supplementary file 3). No adverse events were
4 reported. The patient's global impression of change was 6 (moderately improved).

5 The present case is the first prospective long-term report of DN-DBS in a patient
6 with cerebellar stroke assessed in a blinded fashion. The findings suggest an initial and
7 sustained benefit in tremor and ataxia of unilateral DN-DBS along with long-term safety
8 and a good tolerability profile.

9 To date, only few studies have been designed to assess the effects of cerebellar
10 modulation. A recent study showed that stimulation of dentate nucleus in rats with
11 cortical stroke was associated with motor recovery, probably via intensification of
12 perilesional excitability [4]. Two trials reported improvement in posture and gait in
13 patients with cerebellar ataxia due to stroke after repetitive-TMS stimulation [4]. In
14 regard to cerebellar DBS, there is no study focusing exclusively in ataxia outcomes.

15 In addition to the evidence that cerebellar modulation could restore the altered
16 cortical excitability asymmetry seen between both motor cortices after a chronic
17 cerebellar stroke, structural changes in brain blood flow and metabolism can also be
18 involved in the pathophysiology [4]. Patients with spinocerebellar degeneration showed
19 increased brain blood flow in the cerebellum, putamen, and pons after sessions of
20 cerebellar TMS. A reduction in cerebellar metabolism after 5 sessions of cerebellar TBS
21 in parkinsonian patients was observed through positron emission tomography imaging
22 [5].

23 Despite the consistent result described in the present case, and a reasonable
24 explanation for the improvement, at least in part, based on the restored cortical
25 excitability, the hypothesis on why cerebellar stimulation could change motor

1 symptoms after cerebellar lesions is still theoretical. This is the index case, and larger
2 prospective studies are obviously necessary. The best target into the cerebellum (DN or
3 the dentate-rubro-thalamic tracts or both), the stimulation parameters, and the baseline
4 clinical characteristics predictive of response should be further explored. Interestingly,
5 during the off-stimulation in the last follow-up (4 years) the SARA worsened when
6 compared to the preoperative score, i.e., after the stimulation has been switched off, the
7 worsening of symptoms exceeded the baseline levels, probably reflecting a rebound
8 phenomena. Defining whether the sudden interruption of stimulation affects the
9 cerebellar-cortical circuitry and whether these rebound symptoms also occur when
10 stimulation is tapered off slowly could help explain the mechanism behind the effects of
11 cerebellar modulation

12 Continuous progress in our understanding of brain pathology, connectivity and
13 biomarkers will certainly contribute to the field of movement disorders research,
14 especially regarding new brain targets for neuromodulation. We showed that DN-DBS
15 improved tremor and ataxia in a single patient with cerebellar stroke, and this effect is
16 sustainable over time. The study protocol was safe and well tolerated. Additional
17 comprehensive studies are required to bring evidences for its application in clinical
18 practice.

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1 **Acknowledgement**

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1 **References:**

- 2 [1] R.G. Cury, M.J. Teixeira, R. Galhardoni, V.R. Barboza, E. Alho, C.M. Seixas,
3 G. Lepski, D. Ciampi de Andrade, Neuronavigation-guided transcranial
4 magnetic stimulation of the dentate nucleus improves cerebellar ataxia: A sham-
5 controlled, double-blind n = 1 study, *Parkinsonism Relat. Disord.* (2015).
6 doi:10.1016/j.parkreldis.2015.05.010.
- 7 [2] M.J. Teixeira, R.G. Cury, R. Galhardoni, V.R. Barboza, A.R. Brunoni, E. Alho,
8 G. Lepski, D. Ciampi de Andrade, Deep brain stimulation of the dentate nucleus
9 improves cerebellar ataxia after cerebellar stroke, *Neurology.* 85 (2015) 2075–
10 2076. doi:10.1212/WNL.0000000000002204.
- 11 [3] S.N. Farias da Guarda, L.G. Cohen, M. da Cunha Pinho, F.I. Yamamoto, P.E.
12 Marchiori, M. Scaff, A.B. Conforto, Interhemispheric asymmetry of
13 corticomotor excitability after chronic cerebellar infarcts, *Cerebellum Lond.*
14 *Engl.* 9 (2010) 398–404. doi:10.1007/s12311-010-0176-7.
- 15 [4] C. França, D.C. de Andrade, M.J. Teixeira, R. Galhardoni, V. Silva, E.R.
16 Barbosa, R.G. Cury, Effects of cerebellar neuromodulation in movement
17 disorders: A systematic review, *Brain Stimulat.* 11 (2018) 249–260.
18 doi:10.1016/j.brs.2017.11.015.
- 19 [5] L. Brusa, R. Ceravolo, L. Kiferle, F. Monteleone, C. Iani, O. Schillaci, P.
20 Stanzone, G. Koch, Metabolic changes induced by theta burst stimulation of the
21 cerebellum in dyskinetic Parkinson's disease patients, *Parkinsonism Relat.*
22 *Disord.* 18 (2012) 59–62. doi:10.1016/j.parkreldis.2011.08.019.

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1 **Figure. Representation of the physiology of cerebellar cortical pathway and the**
2 **effect of the dentate-deep brain stimulation after unilateral lesion of the**
3 **cerebellum.**

4 Legend. Panel A displays the excitatory cerebellum-cortico pathway passing through
5 the rubro nucleus and thalamus. There is an ICI between both M1 cortices that is related
6 to preserving the integrity of limbs coordination (panel B). Panel C shows a progression
7 of changes in intracortical motor function over time following a contralateral cerebellar
8 lesion leading toward progressive disinhibition of the primary motor cortex (the ICI of
9 contralesional M1 decreases). Panel D shows the restoration of the interhemispheric
10 asymmetry after DBS of the left DN (ICF of the ipsilesional M1 and ICI of the
11 contralesional M1 both increase). DN = Dentate Nucleus, R = Rubro Nucleus, Th =
12 Thalamus, M1 = Motor Cortex, ICI = Intracortical Inhibition, ICF = Intracortical
13 Facilitation, Green arrow = Excitatory projection, Red arrow = Inhibitory projection
14 (adapted from Teixeira et al., 2015).

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1 **Supplementary File 1.** Cortical excitability parameters during on- and off-stimulation
2 according to the brain hemisphere.

3 Legend. During the on-stimulation condition, the ipsilesional M1 (right hemisphere)
4 intracortical facilitation (ICF) was increased (bold). CE = cortical excitability; ICF =
5 Intracortical Facilitation; MEP = Motor evoked potentials.

6
7 **Supplementary File 2. Video.** At baseline, the patient had cerebellar ataxia, action
8 tremor, dysmetria, and impaired handwriting. She had difficulty performing manual
9 tests such as drawing an Archimedes' spiral. One year and four years after DBS of the
10 healthy DN there is a clinical improvement in terms of dysmetria, writing, drinking.

11
12 **Supplementary File 3.** Evolution of ataxia and tremor over time.

13 Legend. DBS = deep brain stimulation; FTMTRS = Fahn Tolosa Marin Tremor Rating
14 Scale; m = months; SARA = Scale for the assessment and rating of ataxia.

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