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Effects of dentate nucleus stimulation in spinocerebellar ataxia type 3

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Spinocerebellar ataxias (SCAs) are a genetically heterogeneous group of autosomal dominantly progressive diseases that comprise more than 40 distinct subtypes [1]. Currently, there are no approved pharmacological treatments for treating SCAs [1]. Because the cerebellum has many connections with crucial cortical and subcortical structures (e.g., the primary motor cortex, supplementary motor area, and basal ganglia), the modulation of these different neuronal networks through the dentate nucleus (DN) could potentially repair pathological neuronal oscillations and thereby influence motor and sensory integration [2]. Cerebellar deep and superficial (non-invasive) stimulation promotes gait and balance recovery in patients with cerebellar or cortical stroke by acting on cerebello-cortical plasticity [3]. Cerebellar transcranial direct current stimulation can transiently improve symptoms in patients with degenerative ataxias, including SCAs [4]. Here, we tested whether chronic deep DN modulation could reduce symptoms in SCA-3 in a sham-controlled, double-blind n = 1 study.

A 31-year-old female with SCA-3 and refractory ataxia underwent a trial of neuronavigated, repetitive, low-frequency (1 Hz) transcranial magnetic stimulation (rTMS) on the left DN; both the patient and the evaluator were blinded to the treatment. Two (active or sham) stimulation sessions were randomly performed four weeks apart. For the sham procedure, the patient had the coil placed over the scalp and a second active coil was placed on it. This created noise and bumps from the pulses, similar to an active stimulation. The active stimulation resulted in significant improvement in ataxia (25%) and tremor (62.5%). After the patient signed the informed consent, she underwent bilateral DN deep brain stimulation (DBS) in a randomized, double-blind, cross-over design with two 3-month phases (active versus sham) (Fig. 1 illustrates the target) (St. Jude Medical, Plano, Tx, USA). During the active phase, we tested a range of frequencies, between 6 and 150 Hz, and pulse widths, between 60 μs and 210 μs. We observed improvements in tremor (Fahn, Tolosa, Marin Tremor Scale from 23/144 to 16/144; 30% reduction) and cerebellar ataxia (Scale for the Assessment and Rating of Ataxia [SARA] from 15.5/40 to 12.0/40; 22% reduction) during the active phase. No changes were observed during the sham phase. The patient's global impression of change was 5 (moderately better, with a slight but noticeable change). The best settings were bipolar and activated the most dorsal contacts (left DN = 2 mA, 182 μs, 16 Hz; right DN = 1.8 mA, 182 μs, 16 Hz). Stimulation frequencies above 80 Hz worsened gait coordination.

DBS is typically applied to treat medically refractory movement disorders, but it has been poorly studied for cerebellar disorders. The present case is the first to target the DN in a SCA-3 patient. The cerebellum is an important source of excitatory input to the motor cortex via the dentatothalamocortical tract. Degeneration in this pathway reduces excitability in the contralateral cortex; stimulation of the DN increases cortical excitability and consequently promotes motor facilitation [2]. Low-frequency stimulation (which enhances neuronal output) of the dorsal DN has been recently applied in a rat model of neurogenerative ataxia [5]. A frequency of 30 Hz improved motor symptoms; high-frequency stimulation worsened incoordination, as was noted in our case. It has been hypothesized that high-frequency stimulation blocks collateral signals in the vicinity of the stimulated area, thereby affecting fibers associated with motor coordination [5]. Another pre-clinical study reported that low-frequency DN DBS restored motor function after cortical stroke via augmentation of perilesional cortical excitability [2]. In summary, in this study, cerebellar TMS and DBS of the DN improved the patient's SCA symptoms, possibly by strengthening the connections between the cerebellum and several sensory and motor regions.

We observed a modest improvement in the SARA score (3.5 points), but the patient reported subjective slight improvement during the on-phase; for context, a 1-point change in the SARA score is believed to be clinically relevant [1]. The most robust trials of genetic ataxias (SCAs and Friedreich ataxia) showed that riluzole decreased SARA scores by 1.02 points [1]. The mean change in total SARA score in SCA-3 patients receiving a high dose of valproic acid was 2.05 [1].

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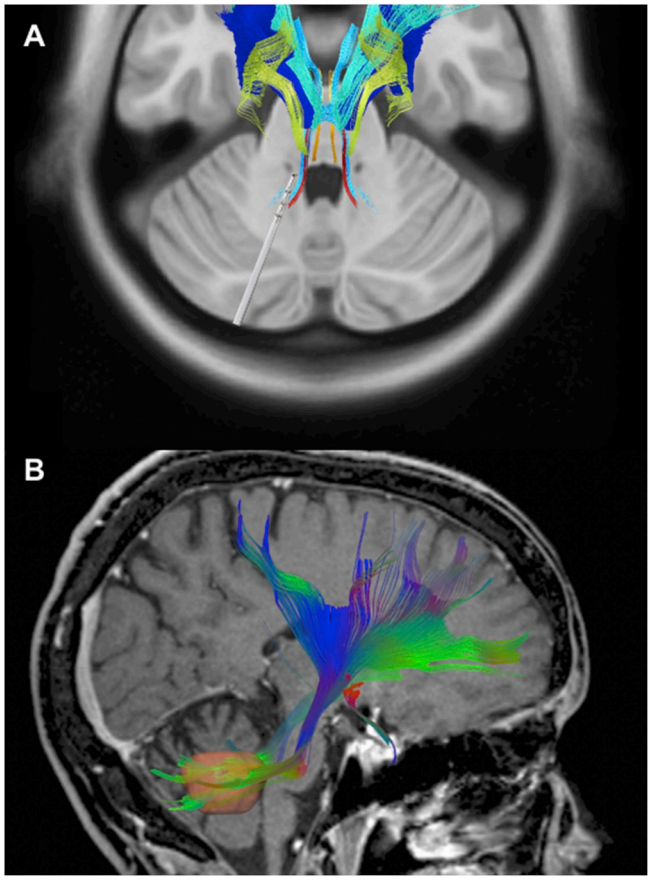

Fig. 1. (A) Three-dimensional demonstration of the DBS electrode displayed in the right cerebellum hemisphere achieving the dentate nucleus. The red and light blue fibers represent the dentate-rubro-thalamic tract derived from a normative structural human connectome. (B) Fiber tractography reconstruction in our neuromodulation laboratory during the dentate-DBS surgery planning. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Low-frequency cerebellar stimulation should be investigated further in larger studies to address whether it effectively treats degenerative ataxias over short- and long-term periods and to better explore the *hot spot* site of stimulation and electric parameters. Measurements of cortical excitability will be necessary, as its unbalancing has been implicated in causing ataxia and DN DBS seems to directly influence them [2]. Finally, studies pertaining to the use of TMS as a tool for predicting surgical responses appear to be promising [2].

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