RESEARCH ARTICLE

Anodal Cerebellar Transcranial Direct Current Stimulation Reduces Motor and Cognitive Symptoms in Friedreich's Ataxia: A Randomized, Sham-Controlled Trial

Gilles Naeije, MD, PhD,[1,2*] Antonin Rovai, PhD,[1,3] Virginie Destrebecq, MD,[1,2] Nicolas Trotta, PhD,[1] and Xavier De Tiège, MD, PhD[1,3]

[1]*Université libre de Bruxelles, UNI—ULB Neuroscience Institute, Laboratoire de Neuroanatomie et de Neuroimagerie translationnelles, Brussels, Belgium*
[2]*Université libre de Bruxelles, Hôpital Universitaire de Bruxelles, CUB Hôpital Erasme, Department of Neurology, Brussels, Belgium*
[3]*Université libre de Bruxelles, Hôpital Universitaire de Bruxelles, CUB Hôpital Erasme, Department of Translational Neuroimaging, Brussels, Belgium*

ABSTRACT: Background: Friedreich Ataxia is the most common recessive ataxia with only one therapeutic drug approved solely in the United States.
Objective: The aim of this work was to investigate whether anodal cerebellar transcranial direct current stimulation (ctDCS) reduces ataxic and cognitive symptoms in individuals with Friedreich's ataxia (FRDA) and to assess the effects of ctDCS on the activity of the secondary somatosensory (SII) cortex.
Methods: We performed a single-blind, randomized, sham-controlled, crossover trial with anodal ctDCS (5 days/week for 1 week, 20 min/day, density current: 0.057 mA/cm^2) in 24 patients with FRDA. Each patient underwent a clinical evaluation (Scale for the Assessment and Rating of Ataxia, composite cerebellar functional severity score, cerebellar cognitive affective syndrome scale) before and after anodal and sham ctDCS. Activity of the SII cortex contralateral to a tactile oddball stimulation of the right index finger was evaluated with brain functional magnetic resonance imaging at baseline and after anodal/sham ctDCS.
Results: Anodal ctDCS led to a significant improvement in the Scale for the Assessment and Rating of Ataxia (−6.5%) and in the cerebellar cognitive affective syndrome scale (+11%) compared with sham ctDCS. It also led to a significant reduction in functional magnetic resonance imaging signal at the SII cortex contralateral to tactile stimulation (−26%) compared with sham ctDCS.
Conclusions: One week of treatment with anodal ctDCS reduces motor and cognitive symptoms in individuals with FRDA, likely by restoring the neocortical inhibition normally exerted by cerebellar structures. This study provides class I evidence that ctDCS stimulation is effective and safe in FRDA. © 2023 International Parkinson and Movement Disorder Society.

Key Words: Friedreich's ataxia; cerebellar cognitive affective syndrome; cerebellar; transcranial direct current stimulation; SARA

Introduction

Friedreich's ataxia (FRDA) is the most common recessive ataxia. To date, no pharmacological therapeutic drug is approved for FRDA despite several trials over the last decades.[1]

FRDA primarily affects dorsal root ganglia, posterior columns, and spinocerebellar tracts of the spinal cord, followed by progressive atrophy of the cerebellar dentate nuclei (DNs) and their efferent fibers targeting the frontoparietal neocortex.[2] A progressive atrophy of

***Correspondence to:** Dr. Gilles Naeije, Hôpital Universitaire de Bruxelles, CUB Hôpital Erasme, Service de Neurologie, 808 route de Lennik, 1070 Anderlecht, Brussels, Belgium; E-mail: gilles.naeije@erasme.ulb.ac.be

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corticospinal tracts also develops later in the disease.[3] Clinically, spinal posterior column impairment is genetically determined and mostly stable over time. Patients become overtly symptomatic when cerebellar ataxia appears.[4] Patients with FRDA also display a wide spectrum of cognitive impairment (eg, deficits in executive function, language, visuospatial abilities, and working memory) that correlates with ataxia severity scores and cerebellar efferent tracts anomalies.[5] Thus, the progressive atrophy of the cerebellum DNs and their efferent tracts targeting frontoparietal neocortical areas plays a key role in the pathophysiology of both ataxia and cognitive impairments in FRDA.

Modulating cerebellum DN activity by applying cerebellar transcranial direct current stimulation (ctDCS) might represent a potential symptomatic treatment option in FRDA. ctDCS is a noninvasive technique that uses low-voltage continuous current for polarity-dependent manipulation of cerebellar cortical excitability to modulate cerebellar efferent dentato-striatal and dentato-thalamo-cortical tracts activities.[6] Computational modeling studies demonstrated the biophysical feasibility of modulating cerebellar activity using ctDCS, with negligible propagation effects to neighboring brain structures.[7] In healthy subjects, a single session of anodal ctDCS increases motors skills,[8] balance, and cognitive performances.[9] ctDCS improves post-stroke aphasia and motor deficits.[10] In movement disorders, ctDCS trials showed positive results in levodopa-induced dyskinesias and writing dystonia.[6] In cerebellar diseases, ctDCS improved essential tremor,[6] and in heterogeneous groups of patients composed of genetic or degenerative ataxias, anodal ctDCS resulted in significant improvement of both motor and cognitive deficits.[11,12]

Anodal ctDCS is thought to increase the inhibition from the cerebellar Purkinje cells to the DNs, reducing the dentatothalamic drive to their neocortical targets leading to reduced neocortical excitability, a phenomenon coined "cerebellar inhibition" (CBI).[13] CBI can be evidenced as a consequence of anodal ctDCS using functional magnetic resonance imaging (MRI; fMRI).[14] Because posterior column atrophy occurs early and is stable over time, investigating the effects of ctDCS on tactile-evoked fMRI responses may provide valuable insights into the study of ctDCS-induced changes in neocortical activity in patients with FRDA. Neocortical somatosensory areas are indeed structurally and functionally connected with the cerebellum and the DNs.[15,16] More specifically, the activity of the secondary somatosensory (SII) cortex is modulated by the level of cerebellar output in healthy subjects,[17,18] as well as in patients with cerebellar pathologies.[19,20] The SII cortex therefore appears as a key neocortical structure to investigate the effects of ctDCS on neocortical activity.

This study aimed at assessing the effects of anodal ctDCS on ataxic and cognitive symptoms in individuals with FRDA. To better understand the effects of ctDCS on neocortical activity, we also investigated using fMRI the effects that anodal ctDCS exerted on SII cortex activity elicited by tactile oddball stimulation. Based on the available literature, we expected that anodal ctDCS would reduce the level of ataxia and cognitive impairment in patients with FRDA in association with a decrease in the fMRI changes elicited by tactile oddball stimulation.

Patients and Methods

Patients

From November 2021 to July 2022, 24 patients with FRDA (13 women, one left-handed; Table 1) were prospectively included. Sample size was based on previous ctDCS studies in cerebellar ataxia and healthy subjects.[21] The Study CONSORT flow diagram can be found in Supporting Information Data S1.

All patients contributed to the study after written informed consent and prior approval of the study by the CUB Hôpital Erasme Ethics Committee (Reference CCB: B4062021000183).

Study Design and Clinical Measures

This study was a single-blind, prospective, randomized, crossover, sham-controlled study based on Benussi's design[12] coupled to fMRI investigations. (Fig. 1).

Patients with FRDA were randomly divided in two groups (group 1, n = 12; group 2, n = 12). At T0, group 1 received placebo stimulation (ie, sham ctDCS), whereas group 2 received effective ctDCS (ie, anodal ctDCS) for 5 days/week during 1 week (T1). After a 12-week (T2) washout, group 1 switched to effective ctDCS for 5 days/week during 1 week (T3), whereas group 2 underwent the placebo stimulation. At the beginning (T0, T2) and end (T1, T3) of each week of stimulation, all patients underwent a comprehensive clinical and fMRI assessment.

TABLE 1 *Characteristics of patients with Friedreich's ataxia*

Patients	Characteristics
Age, median [range] (y)	32 [15–66]
SARA score, median [range]/40	23 [7.5–36]
Age of symptoms onset, median [range]	17 [6–45]
Disease duration, median ± SD (y)	15 ± 7.5
GAA1, median [range]	653 [100–1200][a]

Abbreviations: SARA, Scale for the Assessment and Rating of Ataxia; GAA1, number of GAA1 triplet expansion on the shortest allele.
[a]One patient had a point mutation.

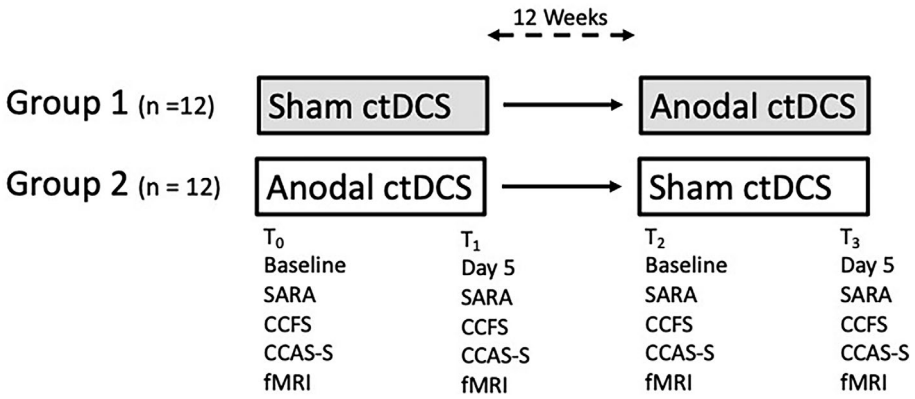

FIG. 1. Experimental design. CCAS-S, cerebellar cognitive affective syndrome scale; CCFS, composite cerebellar functional severity score; ctDCS, cerebellar transcranial direct current stimulation; fMRI, functional magnetic resonance imaging; SARA, Scale for the Assessment and Rating of Ataxia.

The clinical evaluation of cerebellar motor symptoms consisted, at each time point (1 hour before anodal or sham ctDCS), in the evaluation of the Scale for the Assessment and Rating of Ataxia (SARA) score that consists of an eight-item scale assessing gait, stance, sitting, speech, finger chase, nose to finger, upper-limb alternating pronation/supination, and heel to chin maneuver rated on 40 (the higher the score, the higher the impairment), as well as the composite cerebellar functional severity score (CCFS) that combines the nine-hole peg test and the click test (lower scores meant faster performances). Cerebellar nonmotor symptoms were evaluated with the cerebellar cognitive affective syndrome (CCAS) scale.[22] The CCAS scale is composed of 10 items: a semantic fluency task, a phonemic fluency task, a verbal category switching task, a forward digit span, a backward digit span, a cube drawing task, a verbal registration task, a verbal similarities task, a Go/No-Go task, and an affect evaluation. A raw score was obtained for each task, with a minimum passing score (higher raw scores indicating better performances). Three or more failed items of the CCAS scale made a definite CCAS, and two failed items, a probable CCAS and one failed item, a possible CCAS. The four different validated versions of the CCAS scale (A, B, C, D) were used for retest in each patient to avoid learning and test–retest bias.[22]

Cerebellar Transcranial Direct Current Stimulation

ctDCS was delivered by a battery-driven constant current stimulator (Caputron, ActivaDose II) through a pair of saline-soaked surface sponge electrodes of 3 × 3 inches (7.62 × 7.62 cm). For anodal stimulation, the anode was placed on the scalp medially under the inion over the cerebellum area[23] and the cathode on the right deltoid.[7] We applied a constant current of 3.3 mA for 20 minutes to obtain the same current density of 0.057 mA/cm^2 that was used in previous studies performed in patients with ataxia using 2 mA constant current and 2.75 × 1.96-inch (7 × 5-cm) sponges.[12,24,25] For the sham condition, an identical setting in terms of electrode location and stimulation duration was used, except that the constant current was set at 0.2 mA, a current density of negligible effects (0.003 vs. 0.057 mA/cm^2).[26] Patients were blinded to the type of stimulation that was applied, but not the investigators who evaluated the effects of ctDCS and set the ctDCS parameters.

Behavioral Data Analysis

To assess the potential effects of anodal ctDCS on behavioral measures, we used a two-way repeated-measures analysis of variance (ANOVA) with time (before vs. after stimulation) and treatment (sham vs. real stimulation) as within-subject factors. When a significant main effect was reached, paired *t* test was used as post hoc tests for clinical scores before and after stimulation. A *P* value <0.05 was considered significant.

Neuroimaging Investigation

Experimental Design

Patients underwent a 6-minute block-design fMRI paradigm consisting of twelve 30-second alternating blocks (10 brain volumes per block, 120 brain volumes per paradigm) of rest and tactile oddball paradigm derived from Naeije et al.[20] Tactile stimuli were applied using an MRI-compatible pneumatic stimulator.[27] Standards stimuli were applied to the right index fingertip (stimulated area: 1 cm^2, intensity: 3.5 bars, duration: 100 ms, interstimulus intervals: 500 ms), whereas deviants consisted in the simultaneous stimulation of the fingertip and the middle phalanx of the right index finger. Standard and deviant stimuli were randomly interspersed with a ratio of 0.8. Oddball paradigms with low rate of deviant stimuli interspersed in a stream of repeated standard stimuli lead to robust cortical change

detection responses[28,29] that, in the tactile modality, are modulated by cerebellocortical interactions between the cerebellum and the SII contralateral to tactile stimulation (cSII).[19,20,30] Beyond the described interactions between cerebellar function and cSII cortex activity in tactile oddballs,[19,20,30] this paradigm was also chosen for its reproducible recruitment of the cSII cortex in both healthy individuals[28,31] and patients with FRDA.[20]

Data Acquisition

MRI data acquisitions were performed on a hybrid 3-T SIGNA PET-MRI scanner (GE Healthcare, Milwaukee, WI, USA) using a 24-channel head and neck coil (see Lolli et al[32] for details on the MRI sequences).

Data Analysis

fMRI data preprocessing and analyses were performed using the SPM12 software (Wellcome Department of Imaging Neuroscience, London, UK; https://www.fil.ion.ucl.ac.uk/spm/), implemented in Matlab (2017a; Mathworks Inc., Sherbom, MA, USA) using a conventional pipeline detailed by Lolli et al.[32]

First-Level Analysis. Functional images were preprocessed using slice timing correction, realignment, coregistration to the patients' corresponding structural images, normalization to the Montreal Neurological Institute (MNI) template, and smoothing (obtained by applying an isotropic Gaussian kernel of 8-mm full-width at half-maximum). A high-pass filter was applied to remove signal drifts with a period longer than 128 seconds.[32] Statistical analyses were performed in the general linear model (GLM) framework. For each patient, we constructed one GLM for each study time point (T0, T1, T2, T3) that included the preprocessed fMRI data in which the experimental conditions (ie, tactile oddball stimulation vs. rest) were modeled as boxcar functions convolved with the canonical hemodynamic response function. The GLMs also included as covariates of no interest the corresponding six motion parameters obtained from realignment. First-level (within-patient) statistical *T*-contrast maps were then created to identify significant increases in blood oxygen level dependent (BOLD) signal between tactile oddball versus rest conditions. Statistical *t* maps were initially thresholded voxelwise at $P < 0.05$ (family-wise error rate corrected for multiple comparisons; extent threshold, $k = 0$).

Second-Level Analyses. These analyses first aimed at identifying the group-level increases in BOLD signal induced by the tactile oddball stimulation at the baseline of both stimulation conditions (anodal ctDCS: T2 for group 1, T0 for group 2; sham ctDCS: T0 for group 1, T2 for group 2) to demonstrate that the tactile oddball paradigm indeed recruited the expected neural network at baseline and especially the cSII cortex. For that purpose, the individual contrast images issued from the first-level analyses corresponding to the baseline of anodal and sham ctDCS were entered into one single GLM for the second-level analysis that was based on a random effects model. One sample *t* test was then used to assess group-level increases in BOLD signal at baseline (ie, baseline of anodal and sham ctDCS). The significance threshold for the resulting statistical maps was set at $P < 0.05$ family-wise error rate (extent threshold $k = 0$).

Then, given our strong a priori hypotheses about the interaction between the cerebellum and cSII cortex during tactile oddball stimulation,[19,20] we used a region of interest (ROI) approach to assess the effects of ctDCS on that brain area. The ROI was defined as a 5-mm sphere centered around a voxel (MNI coordinates [−45, −25, 18]) located at the cSII cortex identified in a previous fMRI study that validated the pneumatic stimulator used in this work.[27] These MNI coordinates are consistent with SII cortex in neuroimaging data metaanalyses.[33] For each patients' contrast image obtained from the first-level analyses at the different time points (T0, T1, T2, T3), we computed the mean value of contrast across the voxels contained in the cSII cortex ROI. Then, for each patient, we computed the difference between the cSII cortex ROI values before and after anodal (ie, T2 vs. T3 for group 1, T0 vs. T1 for group 2) or sham (ie, T0 vs. T1 for group 1, T2 vs. T3 for group 2) ctDCS. The effect of anodal ctDCS on brain perfusion was finally assessed by comparing the difference in cSII cortex ROI values between anodal and sham ctDCS using a paired *t* test. A *P* value <0.05 was considered significant.

Results

Only 20 patients were able to perform the CCFS. Twenty patients of the 24 initially included did all fMRI sessions. One patient dropped out of the study, one patient refused to pursue fMRI investigation after a single session because of claustrophobia, and two patients were excluded because of an fMRI technical failure for their fMRI after 5 days of stimulation in one session. The final sample of patients with FRDA used for further fMRI analyses was therefore of 10 patients in group 1 and 10 patients in group 2.

Clinical Measures

Table 2 illustrates the effects of anodal and sham ctDCS stimulations on the clinical parameters of patients with FRDA.

We observed a significant time × treatment interaction for the SARA score ($F_{1,23} = 14.93$, $P = 0.0008$,

TABLE 2 *Effects of ctDCS on clinical variables*

	Preanodal ctDCS	Postanodal ctDCS	Presham ctDCS	Postsham ctDCS
SARA, mean ± SD	23.1 ± 9	21.6 ± 9[a]	23.2 ± 9	23.4 ± 9
CCFS, mean ± SD	1.27 ± 0.2	1.23 ± 0.19[a]	1.25 ± 0.17	1.24 ± 0.2
Raw CCAS-S, mean ± SD	89.1 ± 15	99.8 ± 16[a]	91.6 ± 16	92.3 ± 15
CCAS-S failed items, mean ± SD	2.54 ± 1.47	1.54 ± 1.5[a]	2.56 ± 1.9	2.11 ± 1.4

Abbreviations: ctDCS, cerebellar transcranial direct current stimulation; SARA, Scale for the Assessment and Rating of Ataxia; CCFS, composite cerebellar functional severity score; CCAS-S, cerebellar cognitive affective syndrome scale.
[a]Significant difference compared with preanodal ctDCS.

partial $\eta^2 = 0.0251$), the CCAS-S RAW score ($F_{1,23} = 14.84$, $P = 0.0008$, partial $\eta^2 = 0.0147$), and for CCAS-S failed item score ($F_{1,23} = 4.68$, $P = 0.041$, partial $\eta^2 = 0.0020$). Anodal ctDCS led to significant improvement in SARA scores (-1.5 ± 1.3 SD points, $P = 0.0002$), CCAS-S raw scores ($+10 \pm 8.5$ SD points, $P = 0.00003$), and CCAS-S failed item scores (-1 ± 1.3 SD failed items, $P = 0.0004$). Sham ctDCS did not significantly modify SARA scores (-0.2 ± 1.2 SD points, $P = 0.43$), CCAS-S raw scores ($+1.2 \pm 8.4$ SD points, $P = 0.64$), and CCAS-S failed item scores (-0.4 ± 1.1 SD failed items, $P = 0.13$). For the CCFS, we did not observe a significant time × treatment interaction ($F_{1,23} = 2.63$, $P = 0.12$, partial $\eta^2 = 0.058$).

fMRI Analyses

Table 3 and Figure 2 (top) detail the brain regions showing a significant group-level increase in BOLD signal associated with the tactile oddball paradigm at baseline in patients with FRDA.

At baseline, fMRI showed a significant increase in BOLD signal elicited by the tactile oddball stimulation

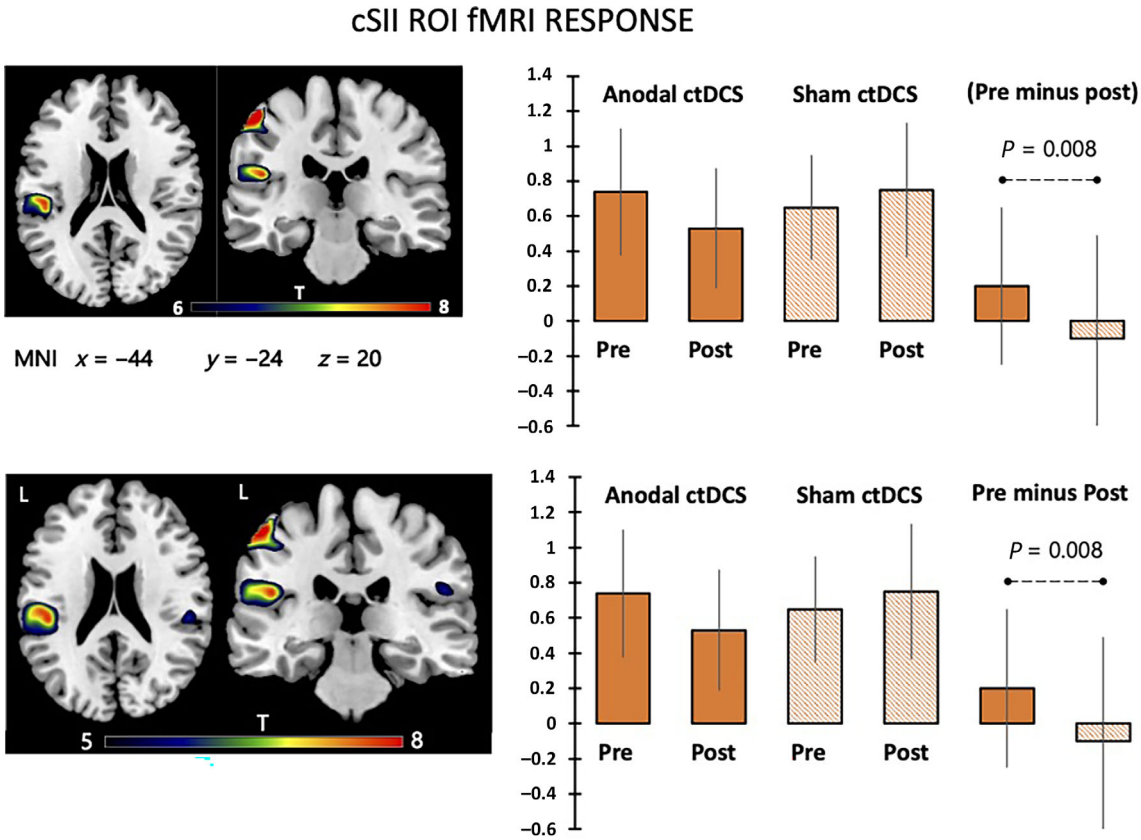

FIG. 2. fMRI response. Top: group-level increases in BOLD signal induced by the tactile oddball stimulation at baseline (fMRI data obtained at baseline before anodal and sham ctDCS were grouped together). Bottom: fMRI response at the cSII cortex ROI for the tactile oddball conditions before (Pre) and after (Post) anodal ctDCS (orange) and sham ctDCS (orange lines). Difference between the difference of fMRI response before and after stimulation for anodal and sham ctDCS. cSII, secondary somatosensory cortex contralateral to tactile stimulation; ctDCS, cerebellar transcranial direct current stimulation; fMRI, functional magnetic resonance imaging; L, left hemisphere; MNI, Montreal Neurological Institute; ROI, region of interest. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 *Brain regions showing a significant group-level increase in blood oxygen level dependent signal associated with the tactile oddball paradigm at baseline in patients with Friedreich's ataxia*

Anatomical region	MNI coordinates [x, y, z]	T values	P values FWE
cSI	[−50, −20, 56]	11.39	<0.0001
cSII	[−46, −24, 20]	7.88	<0.0001
iSII	[52, −26, 22]	5.85	<0.0001

Abbreviations: MNI, Montreal Neurological Institute; FWE, family-wise error corrected; cSI, primary somatosensory cortex contralateral to tactile stimulation, cSII, secondary somatosensory cortex contralateral to tactile stimulation; iSII, secondary somatosensory cortex ipsilateral to tactile stimulation.

at the primary somatosensory (SI) cortex contralateral to the tactile stimulation and at the SII cortex bilaterally both before anodal and sham ctDCS. (Figure 2, top panel)

We found a significantly higher difference in the effects of anodal ctDCS on cSII cortex activity compared with sham ctDCS (anodal, 0.19 ± 0.45 SD; sham, -0.1 ± 0.59 SD; $P = 0.008$). The effect was characterized by a reduced cSII cortex fMRI response elicited by the tactile oddball paradigm after anodal ctDCS. Notably, there was no significant difference in the level of cSII activity at baseline before anodal and sham ctDCS (anodal, 0.74 ± 0.36 SD; sham, 0.65 ± 0.3 SD; $P = 0.35$) (Figure 2, bottom panel).

Discussion

This study shows that anodal ctDCS significantly improves cognitive and motor symptoms in patients with FRDA, and that it reduces cSII cortex fMRI response elicited by a tactile oddball paradigm.

Despite our relatively small sample of patients with FRDA, these results are likely to be valid in other cohorts of patients with FRDA. Indeed, the included patients share the same characteristics in terms of age, age of onset of neurological symptoms, disease duration, SARA score, and size of GAA1 triplet expansion than the average characteristics of the larger published cohorts of patients with FRDA.[34]

Anodal ctDCS improved patients' motor and cognitive symptoms. This finding corroborates previous studies that showed improvement of motor and cognitive performances with anodal ctDCS in cohorts of patients with cerebellar ataxia of mixed origins.[12,21,35] These results provide class I evidence for a role of ctDCS in the care of individuals with FRDA, a disease without validated effective treatments.

However, compared with ctDCS results obtained in populations with cerebellar ataxia of different etiology that included 5% to 11% of patients with FRDA,[12,21] our homogenous population of patients with FRDA displayed specific behavioral changes to anodal ctDCS. Indeed, although the cognitive improvement was similar than in Benussi's study,[12] the motor improvement assessed with the SARA score was on the lower range of previous reports.[11,12] This discrepancy could relate to a combination of clinical, technical, and pathophysiological features associated to FRDA. Clinically, our patients with FRDA had a worse initial clinical SARA score than the heterogeneous ataxic populations studied in previous ctDCS trials.[12,21,35] In those populations, the positive effects of ctDCS tended to be inversely correlated to the initial SARA score, suggesting that anodal ctDCS was more effective in patients who were less severely impaired.[21] The lower SARA score improvement observed in our study could also be related to a lack of sensitivity of the SARA to motor improvement in more severely affected individuals. The SARA is indeed mostly driven by gait and stance items. In wheelchair-bound patients, motor improvement may be more difficult to detect because of ceiling effects. However, the fact that hand dexterity, as assessed by the CCFS, was not significantly improved pleads against a ceiling effect of the SARA. Even if the SARA score improvement was more limited than the cognitive performance, a decrease of 1.5 points on the SARA is still considered as clinically relevant in ataxia studies.[36] Technically, the improvement of ataxic symptoms may also be a function of the number of daily sessions of anodal ctDCS, with larger SARA improvement described after 10 sessions compared with a single session of anodal ctDCS.[12,35] Similarly, repeating anodal ctDCS sessions may also have positive cumulative effects on ataxic symptoms.[12] Therefore, repeating the ctDCS sessions or increasing the numbers of days of ctDCs within a session might be worth trying for patients with FRDA to increase the positive effects of ctDCS on SARA and CCFS scores. Beyond its immediate clinical effects, tDCS may have neuroprotective effects. Animal models indeed showed that tDCS promotes the BDNF pathways involved in neurogenesis and neuronal survival, improves mitochondrial dysfunction, and reduces neurons' oxidative stress,[37] which could also contribute to slow down DN degeneration in FRDA if it is applied repeatedly. The potential benefits of repeating anodal ctDCS sessions and its neuroprotective effects cannot be addressed by our study and warrants dedicated longitudinal cross-sectional studies. In the cerebellum, there is a dichotomy between the posterior cerebellar lobes that modulate cognitive functions and the anterior cerebellar lobes that are implied in motor behaviors.[38] Biophysical model studies showed that the highest electric field and current density during ctDCS are below the stimulating electrode, and thus higher in the posterior cerebellum and

lower in the anterior cerebellum.[7] This current density pattern might therefore also explain why ctDCS is more effective in improving cerebellar cognitive than ataxic symptoms, and why ctDCS for ataxic symptoms might require more sessions to be effective. Finally, the pathophysiology of FRDA can also have differential effects on ctDCS efficiency than in ataxias of other etiologies. Anodal ctDCS is thought to depolarize the Purkinje cells of the cerebellar cortex and increase their inhibitory effect on the DNs and their efferent dentato-thalamo-cortical tracts.[39] Purkinje cells functional impairment or loss, as well as the disruption of cerebellar circuitry, is not homogenous in the different genetic and degenerative cerebellar ataxias and may impact ctDCS efficiency.[40] Different pathophysiological mechanisms may explain the failure of ctDCS to alleviate cerebellar cognitive and motor symptoms in an homogenous group of SCA3[25] and suggest that ctDCS is not a "one-fits-all" solution for cerebellar ataxias. In FRDA, the Purkinje cell population and the cerebellar cortex are generally intact, whereas neuronal loss occurs mostly within the DNs.[3] This leads to a progressive atrophy of its cerebellar efferent tracts, as well as structural anomalies within the superior cerebellar peduncles that correlate with clinical severity.[41,42] Those alterations occur in the cerebellar dentatofugal pathways, which drive the effect of the Purkinje cell inhibition and thus also likely affect ctDCS efficiency. This warrants further investigations in homogenous groups of patients with different kinds of genetic/degenerative ataxias.

Anodal ctDCS is thought to increase the CBI. Evidence for an increase of the CBI came from motor-evoked potential (MEP) studies where anodal ctDCS led to an increase in resting motor thresholds and lower amplitude of MEPs in both healthy subjects and patients with ataxia.[13,35] However, one study also showed an opposite effect of anodal ctDCS in healthy individuals with a decrease of CBI after ctDCS.[43] In our study, we provide fMRI evidence that corroborates an increase of the CBI associated with anodal ctDCS. Indeed, the posterior cerebellar lobes are structurally and functionally connected to the SII cortices and modulate their activity as evidenced by studies using tactile paradigms and resting state investigations in healthy individuals and in patients with cerebellar disorders.[16,17,19,20,44,45] If anodal ctDCS increases the CBI of the cSII cortex, lower cortical activity elicited by identical tactile oddball stimulation should be observed after anodal ctDCS. In our study, patients with FRDA displayed a reduction of 20% to 30% of the cSII cortex fMRI responses elicited by the tactile oddball stimulation. Such reduction parallels closely the range of the effects of anodal ctDCS on the motor cortex threshold and MEP amplitude studied by MEPs.[12,24] Our data therefore suggest that there is a CBI effect induced by anodal ctDCS in a neocortical area known to be highly connected to the cerebellum.[38,44] It is also worth noting that, on a methodological standpoint, our study also offers an alternative to MEP electrophysiological studies that are often found unpleasant by patients with movement disorders.

The major limitation of the study is that investigators were not blinded to the stimulation type (anodal vs. sham), which might have biased the evaluation of the behavioral effects of ctDCS. However, this bias is likely to be limited. First, the SARA, the CCFS, and the CCAS scores have been shown to have a high interrater and test–retest reliability in patients with various types of cerebellar disorder.[46-50] Second, our patients showed the same or less clinical improvement with anodal ctDCS, as well as the same lack of effect of the sham stimulation than in previous double-blind sham-controlled ctDCS studies performed by other groups in patients with mixed causes of cerebellar ataxia.[12,21,24,35] Finally, the significant clinical improvement with anodal ctDCS is also supported by the significant parallel reduction of cSII cortex activity as objectively measured with fMRI.

In summary, this study provides class I evidence that anodal ctDCS reduces cerebellar cognitive and motor symptoms in individuals with FRDA. Anodal ctDCS represents an interesting treatment option in a disease that still lacks approved effective drugs. The positive behavioral effects of anodal ctDCS in patients with FRDA may relate to a partial restoration of the CBI. Further studies need to determine the ideal number of days of ctDCS stimulation, as well as the best lapses between stimulation periods, to achieve maximum clinical benefit in patients with FRDA. ■

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Data Availability Statement

Anonymized data not published within this article will be made available by request from any qualified investigator and after acceptance of institutional (Université libre de Bruxelles and Hôpital Universitaire de Bruxelles) authorities.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Author Roles

Gilles Naeije, MD, PhD, designed and conceptualized study, conducted the experiments, analyzed the data, and wrote the manuscript.

Virginie Destrebecq, MD, conducted the experiments, analyzed the data, and drafted the manuscript for intellectual content.

Antonin Rovai, PhD, analyzed the data and drafted the manuscript for intellectual content.

Nicolas Trotta, PhD, conducted the experiments and drafted the manuscript for intellectual content.

Xavier De Tiège, MD, PhD, drafted the manuscript for intellectual content and provided input for research design and interpretation.

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