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Research Article

Combining Transcranial Direct Current Stimulation and Intensive Physiotherapy in Patients with Friedreich's Ataxia: A Pilot Study

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Abstract

Background: Friedreich's ataxia (FRDA) is a neurodegenerative disorder affecting the dorsal columns of the spinal cord and the cerebellum, with progressive disability and reduced lifespan. No cure is available. Transcranial Direct Current Stimulation (tDCS) is a safe and non-invasive technique leading to modulation of the cortical excitability by application of small-intensity currents directly to the scalp.

Objective: We present a double-blind study in FRDA patients undergoing intensive rehabilitation program (IRP) comparing active (a-tDCS) versus sham-tDCS (s-tDCS).

Methods: We recruited 4 patients: 3F/1M; aged 20.25 ± 3.86 years; disease duration 10.75 ± 3.77 years; GAA1 662.5 ± 159.87, Friedreich's Ataxia Rating Scale (FARS) staging 1 - 4. IRP consisted in 5-weeks of 2 sessions/day. Two-weeks a-tDCS was applied over M1 and cerebellar cortex bilaterally once/day in the active-tDCS. Patients were assessed at pre-/post-treatment with FARS, 6-minute walking test, MiniBEST, BERG.

Results: All patients completed the study and showed functional improvement. tDCS active-arm showed a greater improvement in FARS total score, upright stability section and 6MWT when compared to the control-arm sham-tDCS.

Conclusions: IRP in FRDA results in measurable improvements in functional scales. The effect on walking and upright-stability is potentiated by tDCS to M1/cerebellum that can be due to the cortical stimulation in motor control pathways. Larger RTC are needed to confirm these results.

Keywords: Friedreich's Ataxia; tDCS; Intensive Physical Therapy; sham-tDCS

Abbreviations

FRDA: Friedreich's Ataxia; TDCS: Transcranial Direct Current Stimulation; IRP: Intensive Rehabilitation Program; FARS: Friedreich's Ataxia Rating Scale; 6-MWT: 6-minute Walking Test

Background

Friedreich's ataxia (FRDA) is a neurodegenerative progressive disorder caused by GAA triplet expansion in the FXN gene [1]. FRDA has an early onset with a progressive involvement of the dorsal columns of the spinal cord and progressive ascending CNS damage particularly affecting the cerebellum. FRDA presents with gait impairment, disequilibrium, dysmetria and action tremor, with progressive disability that summoned to heart failure and skeletal abnormalities leads to a reduced lifespan [2].

A wide range of molecules have been used and tested as a treatment in FRDA such as antioxidants, iron chelators, erythropoietin, histone deacetylase inhibitors, interferon gamma [3]; but there is still no cure.

There are currently few studies focusing on rehabilitation in FRDA.

A retrospective study analyzed the effectiveness of the inpatient rehabilitation in modifying the functional state [4]. Leonardi., *et al.* [5] tested the use of a wearable proprioceptive stabilizer in 11 FRDA [5]. Few other studies were qualitative reports highlighting, through the parents' and professionals' perspective, the importance of a wide vision-oriented complex service [6], a holistic approach combined to long-term therapy and home-support [7] and the importance of a training and support addressed to the parents [8].

The transcranial Direct Current Stimulation (tDCS) is a safe and non-invasive technique that applies small-intensity currents directly to the scalp leading to cortical excitability [9]. tDCS has been applied to several neurological conditions with functional and symptomatic improvement.

Pope and Miall [10] have focused their attention on the importance of the non-invasive brain stimulation techniques used to enhance a tonic facilitatory drive onto the motor and cognitive regions of the cortex. Today, there have been several attempts to treat cerebellar symptoms with tDCS. These studies have tested the effect of tDCS by stimulating either the Primary Motor cortex (M1) or cerebellar cortex in patients with ataxia. tDCS has been used as either a single stimulation [11] or a repetitive stimulation for a two-weeks period [12] in patients with ataxia, observing transient symptomatic improvement.

There is not much evidence regarding the effect of physiotherapy treatment in FRDA: we still lack knowledge on the usefulness that physiotherapy treatment can have in a neurodegenerative disorder with a predictable progression.

Our first hypothesis was that an intensive rehabilitation program (IRP) could bring at least transitory benefit to the patients with FRDA. Our second hypothesis was oriented to the possibility that the benefit could be potentiated by the combination of IRP to a cortical stimulation tDCS at the level of M1 and cerebellar cortex bilaterally, as this could act directly by a mechanism of neuronal plasticity enhancement at the cerebello-thalamic-cortical pathway.

We designed a pilot study to assess an intensive rehabilitation program of 5 weeks in FRDA patients with main focus on core stability and trunk control. In addition, within the same period we applied 2 weeks of tDCS localized over the M1 and cerebellum cortex in an active group comparing the effect on a set of functional measures to a control group to which sham-tDCS was applied.

Materials and Methods

Cohort

We recruited 4 patients with a molecularly confirmed genetic diagnosis of FRDA. The patients were recruited at the IRCCS "Eugenio Medea" Research Centre in Pieve di Soligo (Treviso, Italy) (Table 1).

Patients	Sex	Age	DD	FARS stage (0-6)	FARS-EN total pre-treatment (0-117)	GAA1/GAA2	Concomitant treatment	Mobility/ walking aids
1	F	18	7	3	46,33	600/600	Food supplements	Walking frame
2	M	26	14	3	39,33	830/1100	None	Walking frame
3	F	18	8	2	28	470/1230	None	Autonomous
4	F	19	14	4	60,5	750/750	None	Walking frame

Table 1: Demographic and clinical data of the cohort.

Notes: GAA1: Short allele; GAA2: Long allele, DD: Disease duration, FARS: Friedreich's Ataxia Rating Scale; FARS-EN: FARS-neurological examination total score.

The patients were randomly selected to participate in a prospective clinical trial undergoing an IRP. The patients were randomly divided in two groups that consisted in the active group that received the tDCS treatment and the control group that received the sham-tDCS for two weeks. The tDCS was applied in the morning immediately prior the first rehabilitation session of the day. The patients and physiotherapist were not aware of the group distribution.

The inclusion criteria included: FRDA genetic diagnosis, FARS scale stage 1 - 4 relating to patients with a mild to moderate disability with autonomous walking or need for a walking frame; free of any contraindication of using tDCS (such as metallic devices) and willing to participate in the study.

The stimulation procedure was performed by MV. The quantitative assessment and the IRP were administered by VM and JC.

The study was approved by the institutional ethics committee (IRCCS E. Medea - Associazione La Nostra Famiglia - Bosisio Parini, LC). Written informed consent was obtained from all the patients and the study was performed in accordance to the Declaration of Helsinky.

Assessment protocol

Patients were assessed before and after completing the IRP with quantitative tests such as Friedreich's Ataxia Rating Scale (FARS) [13], 6-minute walking test (6-MWT) [14] and scales for the equilibrium assessment as MiniBESTest [15] and BERG scale [16].

Intensive rehabilitation program

The IRP consisted of two daily sessions of physical therapy training of 45 minutes each for 5 days per week. Three patients underwent 5 weeks of physical therapy training, whereas one of them did only 4 weeks out of five for personal reasons (Figure 1). The rehabilitation sessions were executed from the same therapists (VM and JC). The IRP was designed to enhance and support the motor abilities, core stability and trunk control. It consisted on core stability exercises aiming to work on postural stability, alignment of the different segments of the body and tapis roulant sessions.

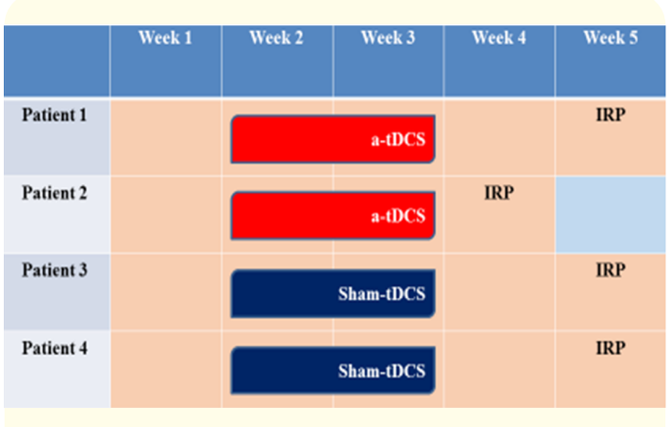

Figure 1: Study design. The cohort of the patients underwent a period of physical therapy training of 4-5 weeks. The active arm (Patients 1 and 2) underwent two weeks of a-tDCS and the control arm (Patients 3 and 4) underwent the sham-tDCS. Notes: IRP: intensive rehabilitation program, tDCS: transcranial Direct Current Stimulation.

tDCS

Patients underwent two weeks of stimulation with anodal tDCS (a-tDCS) or sham-tDCS (s-tDCS) (Figure 1) once a day for five days. The a-tDCS (or s-tDCS) were always executed immediately before the morning physical therapy training session. The areas of tDCS stimulation selected were the M1 and cerebellar cortex bilaterally. During the first week of stimulation the two channel anodes were placed in the M1 bilaterally, followed by the cerebellar cortex bilaterally in the second week. The cathode channel was placed on the right deltoid muscle in both weeks. A HDCkit of Portable and Programmable DC stimulator was used (Newronika S.r.l., Italy). The cortical electrodes were encapsulated into sponge electrodes (50 x 50 mm) and Newronika conductive gel was used as a medium in contact to the scalp over the M1 and cerebellar cortices. The arm electrode was encapsulated into another sponge electrode (85 x 60 mm) and the same gel was applied. The stimulation for the a-tDCS group was ramped on over 5 seconds up to 2mA and maintained for 20 minutes. The sham stimulation was initially ramped on similarly to the a-tDCS group but maintained for only 5% of the treatment length (circa 1minute) and afterwards the current would turn off automatically.

Statistical analysis

Descriptive analysis was performed to compare the differences between the pre- and post-treatment results in all the patients and also for each group separately. The whole cohort size and the groups size were not big enough to perform any inference testing.

Results

The IRP was tolerated by all the patients. The application of the a-tDCS and sham-tDCS was well tolerated in both groups and none of the patients required to stop or interrupt it. The patients reported only mild side effects due to the direct current such as metallic taste in the tongue, itchy sensation, and we observed erythematous reaction on the right arm in correspondence to the cathode site application.

We confronted the data of all the patients that underwent the study by comparing the scores of pre-vs post-treatment (Table 2a).

We observed a general improvement in all the patients in the FARS- neurological examination section (FARS-NE) score, total FARS score, FARS-upright stability subsection and FARS - upper limb coordination, the 6MWT, and the equilibrium scales such as MiniBEST and BERG (Table 2a and Figure 2a). Although the disease staging did not change, we observed either improvement or unchanged scores in other of the FARS sections such as bulbar, peripheral and lower and upper limb coordination at the end of the study (Table 2a).

Comparing both the study groups, main differences were observed in the FARS-EN total, FARS-EN upright stability and the 6MWT (Table 2b). The comparison between the two study groups in the FARS-EN total score and the FARS-EN subsection on stability is reported in figure 2b and 2c for the group comparison. The

	Patient 1		Patient 2		Patient 3		Patient 4		Cohort Mean ± SD	
FARS	T0	T1	T0	T1	T0	T1	T0	T1	T0	T1
Staging	3,00	3,00	2,00	2,00	2,00	2,00	4,00	4,00		
ADL	13	13	11	11	4	4	10	10		
EN-Bulbar	2,5	2,5	1	1	1	1	3,5	3,5		
EN-UL	12,5	10	7	2,5	11	4,5	10	9	10,13 ± 2,32	6,5 ± 3,58
EN-LL	6	7	2	2	1	1	12	11,5	5,25 ± 4,99	5,37 ± 4,85
EN-PNS	8	7	12	12	6	6	11	11	9,25 ± 2,75	9 ± 2,94
EN-Upright stability	17,33	14,5	17,33	14	9	9	24	23,5	16,91 ± 6,14	15,25 ± 6,03
EN-Total score	46,33	41	39,33	31,5	28	21,5	60,5	58,5	43,54 ± 13,59	38,12 ± 15,74
6MWT	198	294	81,2	162	508,2	510	41,4	60	207 ± 211	256,5 ± 194,26
MiniBEST	5	8	7	10	16	19	0	1	7 ± 6,68	9,5 ± 7,41
BERG	31	36	38	43	47	52	6	7	30,5 ± 17,59	34,5 ± 19,46

Table 2a: Presentation of the clinical assessment data pre-treatment (T0) and post-treatment (T1) for each patient and the mean of the whole cohort.

Notes: FARS: Friedreich's Ataxia Rating Scale; ADL: Activities of Daily Living; EN-UL: Neurological Examination Upper Limb Coordination; EN-LL: neurological Examination Lower Limbs Coordination; EN-PNS: Neurological Examination Peripheral Nervous System; 6MWT: 6-minute Walking Test; SD: Standard Deviation.

inter-group mean difference was for FARS-EN upright stability (σ mean T1-T0 is -3.08 in the a-tDCS versus -0,25 in the s-tDCS) and for FARS-EN total score (σ mean T1-T0 is -6.58 in the a-tDCS versus -4,25 in the s-tDCS).

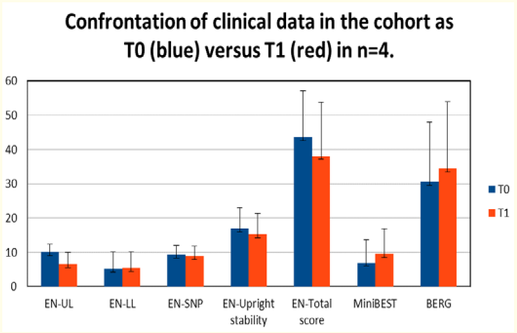

Figure 2a

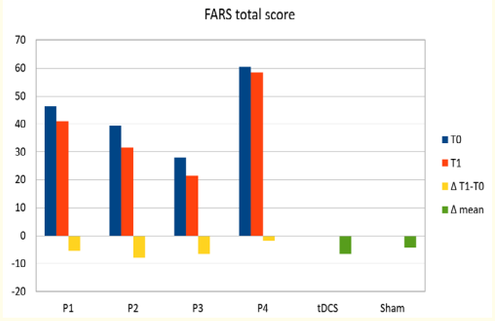

Figure 2b

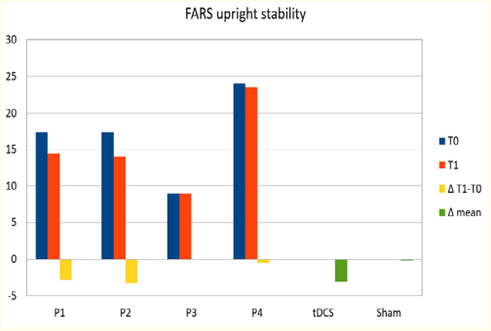

Figure 2c

Figure 2: (A) Confrontation of clinical data in the cohort of patients (n=4) baseline (T0) versus after-treatment (T1). (B) FARS total scores in T0 versus T1 provided for each patient and for each study group as a-tDCS versus Sham-tDCS. (C) FARS upright stability section scores in T0 versus T1 provided for each patient and the mean difference for each study group as a-tDCS versus Sham-tDCS. Notes: EN-UL: FARS neurological examination upper limbs; EN-LL: FARS neurological examination lower limbs; EN-SNP: FARS neurological examination peripheral nerve system.

All four patients achieved an improvement in the 6MWT. A larger improvement was achieved in the a-tDCS group when compared to the control group of s-tDCS (Table 2b and Figure 3a) (σ mean T1-T0 is 88,4 m in the a-tDCS versus 10.2 m in the s-tDCS). A minimal improvement in 6MWT of only 1.8 m was observed in patient 3. We explained the minimal improvement in the distance length by the observation that she managed to improve the stability in the walking pattern, being the only autonomously walking patient.

	a-tDCS (mean)		Sham-tDCS (mean)	
FARS	T0	T1	T0	T1
EN-UL	9,75	6,25	10,5	6,75
EN-LL	4	4,5	6,5	6,25
EN-SNP	10	9,5	8,5	8,5
EN-Upright stability	17,33	14,25	16,5	16,25
EN-Total score	42,83	36,25	44,25	40
6MWT	139,6	228	274,8	285
MiniBEST	6	9	8	10
BERG	34,5	39,5	26,5	29,5

Table 2b: Presentation of the clinical assessment data pre-treatment (T0) and post-treatment (T1) for each group (a-tDCS versus sham-tDCS group).

Notes: FARS: Friedreich's Ataxia Rating Scale; ADL: Activities of Daily Living; EN-UL: Neurological Examination Upper Limb Coordination; EN-LL: Neurological Examination Lower Limbs Coordination; EN-PNS: Neurological Examination Peripheral Nervous System; 6MWT: 6-minute Walking Test; SD: Standard Deviation.

All the patients improved when considered the total score in the MiniBESTest scale (Figure 3b) and in the BERG scale (Figure 3c). In particular, 3 patients showed an improvement in 3 different items (out of 14) in the MiniBESTest scale. The improved items were variable, with no particular distribution and including all the four main sections of the MiniBESTest as anticipatory items, reactive postural control, sensory orientation and dynamic gait.

The results of the BERG scale showed a concomitant improvement in at least two patients with no additive effect of the a-tDCS when compared to s-tDCS group.

The MiniBESTest and BERG scale showed a general improvement in all the four patients but no intergroup differences (Figure 3b and 3c).

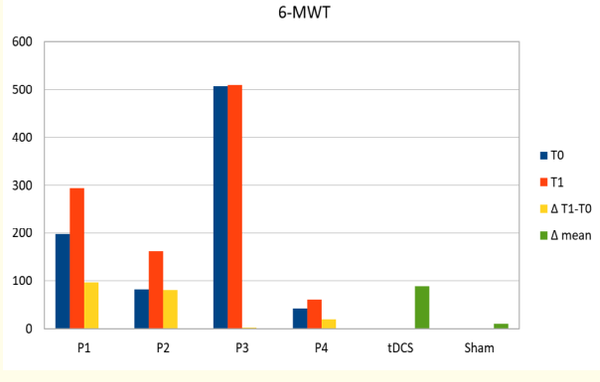

Figure 3a

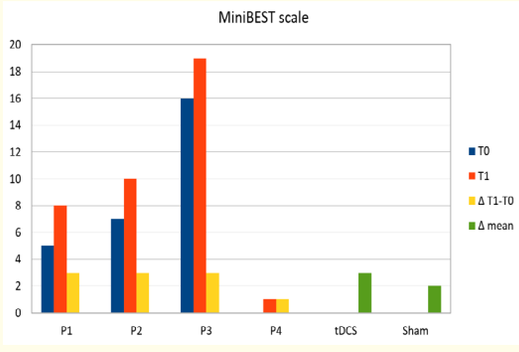

Figure 3b

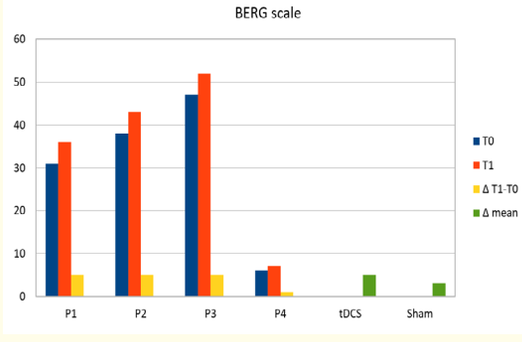

Figure 3c

Figure 3: Confrontation (A) 6MWT, (B) MiniBEST and (C) BERG scale values in T0 versus T1 provided for each patient and the mean difference for each study group as a-tDCS versus Sham-tDCS. Note: 6MWT: 6-minutes walking test.

Discussion and Conclusion

We designed a double blind pilot RCT study in FRDA patients undergoing IRP with neuromodulation on M1 and cerebellar cortex as compared to the control arm on sham-tDCS.

This study was performed to investigate the benefits of a 5 weeks period of IRP in FRDA and whether adjuvant a-tDCS could potentiate the clinical improvements as compared to the control arm.

We demonstrated an overall improvement in all the patients participating in the study. In addition to the IRP beneficial effects, here we demonstrated how the a-tDCS in the active arm led to improvements in functional areas related to the disease severity, the upright stability and in the distance walked in 6 minutes.

The effect of an IRP period is followed by positive effects in all the patients. The differences observed between the two groups in our study could eventually be explained by the potentiation of the cortical neurons corresponding to the M1 and the cerebellar cortex stimulated by a-tDCS involved in the motor control pathways.

Speculations have been made on the possible effect of the tDCS on the cortical activity and cortical output, as this could possibly help restoring the cerebello-thalamo-cortical pathways [17]. Similarly, the cerebellar tDCS might lead to a restoration of cerebellar-brain inhibition pathway [12].

We observed improvement in the gait similarly to Pozzi., et al. [17] on a study on ataxia patients with M1 anodal tDCS stimulation [17]. Subsequently, the improvement in the standing posture is supported by studies in healthy controls (HC) [18] and in ataxia patients [19]. We stimulated two different cortical areas: cerebellar and M1 and observed improvement in disease severity scores. The bi-cortical stimulation has been reported in a patient with ARCA3 cerebellar ataxia [19] in whom disease severity was modified. We did not observe changes in postural tremor and this is in contrast to other studies [19,20].

We believe that the tDCS treatment duration of two weeks was responsible for the enhancement effect in the outcome measures, as confirmed by another double blind randomized sham controlled trial [12]. The two weeks tDCS treatment exerts a consistent reinforcing and lasting effect in the outcome measures as compared to a transient improvement of the cerebellar symptoms due to one single session of tDCS [11].

The neuromodulation has proved to be useful in movement disorders [21] and in particular in the cerebellar ataxias, focal dystonia, essential tremor and Parkinson's Disease (PD). However, these results come from few clinical trials, with small sample sizes and perhaps publication bias in favor of the positive results studies publications. Yet, it has been reported that the cerebellar ataxias can gain some benefit from tDCS in terms of postural tremor, action tremor, dysmetria and balance [11,12,19,20,22]. On the contrary, other studies report no changes [23,24] or simply improvements in essential tremor [25]. The tDCS has been successfully used as a treatment attempt in neurological and psychiatric conditions such as chronic pain, depression, chronic migraine, fibromyalgia, post-stroke rehabilitation and cognitive deficiencies [26]. Interestingly, tDCS had been applied to treat symptoms such as dysphagia in stroke and multiple sclerosis patients [27], stroke-related breathing difficulty [28], levo-dopa induced dyskinesias in PD [29] and chronic tinnitus [30].

The neuromodulation effects on the training sessions has been demonstrated both in HC and in patients. Angius*., et al.* [31] have reviewed the ergogenic effects of tDCS in HCs during exercises concluding benefits on the submaximal intensity performed task relatively due to the tDCS effect. These results confirm the effect of the M1 cortical excitability in the motor task, by suggesting that any modification of the brain function can subsequently lead to behavior modification. Interestingly, Hendy., *et al.* [32] proposed a protocol of combined M1- tDCS and physiotherapy treatment targeting balance and gait in 6 weeks with a frequency of 3 times per week but so far no results have been published.

The combination of tDCS with rehabilitation has been discussed by Malerba., *et al.* [33] in the context of the role of a biophysical model in the post-stroke recovery attempts. The rehabilitation of the post-stroke recovery plays an important role in facilitating the relearning of the motor skills apparently due to the synaptic neuroplasticity [33]. We believe that the biophysical model could eventually be applied to the movement disorders including neurodegenerative conditions, where tDCS could facilitate the rehabilitative interventions by improving recruitment activity at the pyramidal cells layer on the M1 with subsequent neural network function recovery. This network is thought to be consolidated due to the neuroplasticity use-dependent and leads to a network state able to relearn [33].

The tDCS is a safe and easy technique [26] and leads to the increase of spontaneous neuronal activity of the cortex via anodal stimulation. The cerebellar tDCS leads to biological effects as measured through physiological and behavioural data, which could be explained by either neuroplasticity or neurotransmitter changes [9,34] eventually resulting in modulation of the cerebellar-thalamo-cortical projections [35], motor learning [36] and gait adaptation [37].

The study consists of a limited group size. The operator-dependent data can have an influence in the results, but we assume that experienced operators and the double-blinded controlled design of the study helped to avoid the operator-dependant bias. Long-term effects of neuromodulation has yet to be assessed in addition to the eventual frequency of neuromodulation repetition in combination to the IRP with the intent to halt the disease progression.

In conclusion, facing a neurodegenerative condition such as FRDA, characterized of progression and a large impact on the quality of life, it is of paramount importance, while an effective therapy is still lacking, to offer alternative treatments capable of attenuating the disabling disease manifestations. The IRP coupled with M1 and cerebellar cortex tDCS in this perspective can play a positive role. The neuromodulation provided by a safe technique such as tDCS combined to IRP can be proposed as a potential remedy for selected impairments associated with the disease. We still don't

know the retention interval of the observed improvement and are prevented form generalising the results of our small pilot trial by the short duration and minimal patients number: longer and larger trials should address this issue.

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Conflict of Interest

The authors declare no conflict of interest.

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