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TRANSCRANIAL DIRECT CURRENT STIMULATION (t-DCS) AS ADD-ON TO NEUROREHABILITATION OF PISA SYNDROME IN PARKINSON'S DISEASE: A RANDOMIZED CONTROLLED TRIAL

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La fatica non è mai sprecata,
soffri, ma sogni.

Pietro Mennea

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ABSTRACT

Background: Pisa syndrome (PS) is a lateral trunk flexion frequently associated to Parkinson's disease (PD). The management of PS is still a challenge for the physicians because it poorly responds to the anti-parkinsonian drugs, and the improvement achieved with neurorehabilitation or botulinum toxin injections tends to fade in 6 months or less. Transcranial direct current stimulation (t-DCS) is a non-invasive neuromodulation technique, which showed promising results in movement disorders. The aim of our study is to evaluate the role of bi-hemispheric t-DCS as add-on to neurorehabilitation in PS.

Methods: Twenty-eight patients with PD and PS (21 male, age 72.9±5.1 years, PD duration 9.3±7.4 years, PS duration 3.0±1.9 years) received a 4-week intensive neurorehabilitation treatment and were randomized to receive t-DCS (t-DCS group, *n*=13), 5 daily sessions (20 minutes - 2 mA) with cathode over the primary motor cortex (M1) contralateral to PS, and anode over the M1 cortex ipsilateral to PS, or sham group (sham group, *n*=15). At baseline (T0), end of rehabilitation (T1) and 6 months later, patients were evaluated with trunk kinematic analysis in static and dynamic conditions, UPDRS-III, FIM, and VAS for lumbar pain rating. At T0, the evaluations were completed by an EMG study of trunk muscles.

Results: The study groups were comparable for clinical/demographic features and EMG phenotypes. When compared to sham group, t-DCS group achieved better results in several variables: overall posture (p=0.014), lateral inclination (p=0.013) of trunk during upright standing position, total range of motion (ROM) of the trunk (p=0.012), ROM of bending ipsilateral to PS (p=0.037), and ROM of anterior trunk flexion (p=0.014). The improvement in the overall trunk posture in upright standing position was persistent in t-DCS group at 6 months (T2 vs. T0: p<0.050). UPDRS-III scores decreased after rehabilitation (p=0.001), without significant differences between t-DCS and sham groups (p=0.942). In contrast, FIM score and lumbar pain intensity improved the most in t-DCS group when compared to sham group (p=0.048, and p=0.017 respectively). The EMG pattern was not a predictor of the efficacy of the t-DCS treatment.

Conclusions: Our data supports the use of neuromodulation with t-DCS as add-on to neurorehabilitation for the treatment of patients affected by PS in PD. t-DCS is a non-invasive and repeatable approach that proved effective even in those patients with an EMG pattern not amenable to botulinum toxin injections.

INTRODUCTION

Axial disorders are frequent complications of Parkinson's disease (PD) and they can lead to postural deformities and balance impairments[1]. The most prevalent postural disorders of PD are represented by camptocormia, antecollis, scoliosis, and Pisa syndrome (PS)[1–3].

The pathogenesis of these disorders has not yet been completely elucidated, and it is characterized by a complex interlacement between central and peripheral mechanisms.

The first report of PS dates back in 1972, when Ekbom et al. described a case series of three patients who developed a lateral trunk flexion in close temporal relationship with neuroleptics assumption[4]. The roster of drugs associated with an acute/subacute onset of PS is huge and constantly growing, and it includes: antidepressants (mirtazapine, sertraline), cholinesterase inhibitor (rivastigmine, galantamine, donepezil), neuroleptics (tiapride, clotiapine, clozapine, aipiprazole, butyrophenone, paliperidone, quetiapine), dopamine agonists, (pramipexol, ropinirole, pergolide), lithium, valproic acid, and betahistine[4–18]. Nonetheless, PS was described as well in patients with neurodegenerative disorders, and in particular in PD and parkinsonism without drugs exposure[19,20].

The prevalence of PS is around 8.3% (9.3% in women and 6.4% in men) when calculated in a psychogeriatric population, and it is 8 to 8.8% when populations of PD patients were considered[21–23].

Formal diagnostic criteria for PS are not available, and the diagnosis is therefore based on the following clinical features (Figure 1)[24–26]:

- presence of a lateral flexion of the trunk with a homogenous angle between sacrum and spinous process of the 7th cervical vertebra;
- association of an ipsilateral rotation of the trunk around the sagittal axis that leads to a higher and anterior position of the shoulder contralateral to the side of trunk deviation;
- the postural disorder worsens during standing position, sitting position and gait;
- the postural disorder improves in supine position;
- disregard of patients for the postural disorder.

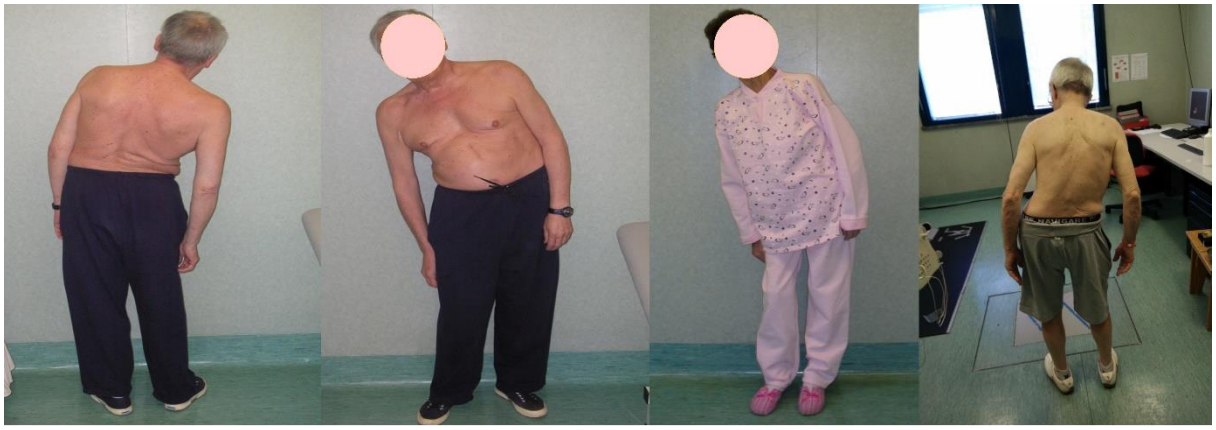
The fluctuation of the postural alteration during static (supine position vs. upright standing position) and dynamic conditions appears to be crucial to differentiate PS from scoliosis.

A lateral trunk deviation of at least 10° is commonly accepted for the diagnosis, although higher or lower cut-offs were used in the past[22,27–29]. According to the degree of the lateral trunk

flexion, PS can be further divided in mild (less than 20°) or severe (more than 20°) phenotypes[27,28]. Considering that PS is often associated to other postural disorders[30], the real severity of the lateral trunk flexion may be difficult to calculate, therefore we suggest to monitor the patient over time with photos, videos, goniometric measures and, where possible, with instrumental analysis of movements[31].

Patients with PD and PS showed some typical clinical and demographic features when compared to PD patients without postural alterations: they are older, PD is longer in duration, more severe and with a more pronounced asymmetry of motor symptoms[23,26]. The parkinsonian symptoms involving the upper limbs as well as gait impairment are more severe in PD patients with PS[32,33]. Moreover, they are characterized by a higher incidence of falls, arthrosis, osteoporosis, orthopedics diseases and pain, specifically lumbar and lower back pain, which is reported in up to 75% of patients with PD and PS[23,31].

Figure 1 – Examples of Pisa syndrome in three Parkinson's disease patients



All patients provided an informed consent for the above pictures.

- *Pathophysiology of Pisa syndrome*

Several pathophysiological mechanisms have been hypothesized for the genesis of PS in PD. The initial idea that PS represents an atypical dystonia has been gradually substituted by the theory in which "central" and "peripheral" mechanisms are involved[34]. A central alteration, namely an asymmetric basal ganglia outflow, seems to play a major role in PS pathophysiology. Pre-clinical evidence suggests that an asymmetric dopaminergic signal leads to a postural disorder toward the side of the most impaired striatum. Indeed, animals exposed to cholinergic or electric stimulation of the caudate nucleus developed a postural rotation away from the stimulated side[35]. In the rat, striatal injection of a D1-D2 agonist led to a contralateral postural deviation, and this observation was prevented by a pre-treatment with a dopaminergic

antagonist[36]. In contrast, rats with nigro-striatal experimentally induced denervation developed an ipsilateral postural deviation, which severity strictly correlated with the degree of the induced denervation[37,38]. Moreover, subthalamic nucleus ablation was able to induce a contralateral postural deviation in healthy monkeys, or it was able to prevent the postural alterations in the parkinsonian rat model based on the nigro-striatal induced denervation, as previously described[39,40].

These observations are consistent with clinical evidence. PS is more prevalent in PD patients with high motor asymmetry[26]. Moreover, in around 70% of PD patients the side of PS is toward the less impaired parkinsonian side at onset[23,26,31,41,42].

In line with pre-clinical data, it was reported that unilateral therapeutic surgery strategies, such as pallidotomy and subthalamic nucleus ablation, were complicated by the onset of a PS directed away from the surgical side[43,44].

Altogether, animal and human data support the hypothesis of an imbalance in the dopaminergic outflow between left and right basal ganglia, leading to a postural trunk deviation directed toward the more denervated striatum (namely the less impaired side of PD).

However, the observations that in around 30% of PD patients the side of PS is not the less affected one, and the well described onset of PS after administration of non-dopaminergic drugs suggest that other mechanisms are involved.

Indeed, an imbalance in the neurotransmitters implied in trunk control has been described. Patients with PS are characterized by altered levels of noradrenaline, serotonin as well as increased acetylcholine levels that are coupled with a dopamine deficit[45].

These findings are corroborated by the association of PS with other neurodegenerative disorders (Alzheimer Disease and Multiple System Atrophy)[46,47] as well as by the correlation between PS onset and the administration of several drugs, especially the cholinesterase inhibitors[17,48].

Finally, Vitale et al. and Di Lazzaro et al. described a vestibular deficit, ipsilateral to the side of PS, in parkinsonian patients with PS, which could explain the altered perception of verticality as well as the indifference of patients toward the postural misalignment[41,49].

The peripheral mechanisms are less supported by scientific evidences, and they rely on the hypothesis that a primitive muscolo-skeletal alteration is involved in PS pathophysiology. Although no histological studied have been published in PS, paraspinal muscles biopsy performed in patients with PD and camptocormia showed unspecific myopathic alterations, namely a combination of fibers loss with fibers hypertrophy[50]. Electromyographic (EMG) studies in PS in PD did not show neurophysiological signs typical for primary muscles

disease[26,28,42,51]. Neuroimaging findings are consistent with an atrophy of the paraspinal muscles in patients with PS; hypotrophy appeared to be more pronounced towards the side of trunk deviation although conflicting results were published on this topic[26,28,42,51].

- *Electromyographic patterns of trunk muscles activation in Pisa syndrome*

In the past years, a great effort was made to classify the pattern of muscular activation of patients affected by PS and PD.

Di Matteo et al. (2011) described two different phenotypes: i) a tonic activation of the longissimus thoracis muscle (between T12 and L1) ipsilateral to PS during upright standing position that does not recede during contralateral trunk bending, resulting in an EMG dystonia-like coactivation of left and right paravertebral muscles, and ii) a tonic activation of the longissimus thoracis muscle contralateral to PS during upright standing position, without muscles coactivation[42].

Tassorelli et al. (2012) described a tonic, persistent, activity in the upright position of the abdominal oblique muscle and of the paraspinal thoracic muscle (T6-T7) ipsilateral to PS, while muscle activity was suppressed in the same muscles on the opposite side. It is worth noting that the described asymmetric tonic activity normalized in supine position, and this EMG finding is well paralleled with the clinical improvement of PS when patients lie supine[26].

Moreover, if an extensive EMG evaluation is used (paraspinal lumbar muscles, paraspinal thoracic muscles, abdominal oblique muscles, iliopsoas, rectus femoris), the following PS EMG phenotypes could be described[51]:

- Pattern I: hyperactivity of lumbar paraspinal ipsilateral to trunk leaning side, and:
    - Subtype 1: associated to hyperactivity of thoracic paraspinal ipsilateral to trunk leaning side
    - Subtype 2: associated to hyperactivity of thoracic paraspinal contralateral to trunk leaning side
- Pattern II: hyperactivity of lumbar and thoracic paraspinal contralateral to trunk leaning side, with hyperactivity of non-paraspinal muscles ipsilateral to trunk deviation (rectus femoris, iliopsoas, abdominal oblique).

Even though the hypothesis that PS is a pure trunk dystonia is now abandoned, the dynamic EMG evaluation during active trunk movements (namely left and right lateral bending) is consistent with a dystonic activation of lumbar paraspinal muscles (Pattern I) or of non-

paraspinal muscles (Pattern II), associated or not with a compensatory activation of contralateral paraspinal muscles[51]. Moreover, it was described that the EMG pattern may change as the disease advances. Thus, dystonia-like features predominant at PS onset may disappear in the late stages of PS when muscles hypotrophy becomes prevalent[26,42,51].
A dynamic EMG evaluation of the trunk is therefore suggested in the early stages of PS in PD because it can discern between different EMG phenotypes, it is useful in the differential diagnosis process with trunk dystonia, and it is a mandatory screening tool to decide whether a patient will benefit from botulinum toxin injections[2,24,31,52].

- *Therapeutic management of Pisa syndrome*

The management of PS is still a challenge for the physicians[20]. PS poorly responds to antiparkinsonian drugs, although studies specifically designed to assess this topic are lacking.

Neurorehabilitation represents one of the fundamental approaches to PD and to postural disorders in general, not only for the treatment of the motor symptoms themselves, but also to improve quality of life and autonomy in the activity of daily living[53].

Mainly delivered with the Bobath approach and with trunk exercise in closed kinetic chain, the rehabilitation treatment in PS has been assessed in four studies[54–57]. The largest cohort of patients with PS and PD was enrolled in 2010 by the group of Bartolo et al. The Authors demonstrated how a 4-week rehabilitation program improved trunk posture in upright standing position as well as trunk range of motion, although the effects tended to fade over 6 months[54].
Botulinum toxin type A (BTx-A) injection, in association or not with rehabilitation, proved effective in PS in two randomized controlled trials as well as in several case series[28,31,52,58,59].
Bonanni et al. in 2007 treated 9 PS patients with injections of BTx-A or placebo in the lumbar paraspinal muscles (L2-L5 levels) ipsilateral to trunk deviation, and demonstrated a reduction in lateral trunk bending from 50% to 86% in the active group[28].
In 2014, the group of Tassorelli et al. studied the efficacy of a combined therapy with BTx-A in association to a rehabilitation program. Lateral trunk flexion improved at the end of a 4-week rehabilitation treatment, and this achievement was maintained at 3 months, but not at the 6-month follow-up[31]. Along with the postural improvement, BTx-A injection ameliorated lumbar pain associated to PS[28,31].
Data from the literature suggest that Deep Brain Stimulation (DBS) may exert positive effects in PS and PD, even though these reports are case series, or insights derived from sub-groups

analyses of PS patients enrolled among a wider PD cohort. The suggested targets for DBS are represented by the bilateral globus pallidus internus[60], the bilateral subthalamic nucleus[61–64], and the pedunculopontine nucleus contralateral to side of PS[65,66]. The invasiveness of the procedure and the well-known contraindications to DBS are the main limitations of this approach for PS in PD[67].

Lidocaine injections[68], oculomotor rehabilitation[69], and spinal cord stimulation[70] were tested in PS, but data is scarce and definitive conclusions are not possible.

Transcranial direct current stimulation (t-DCS) is a non-invasive neuromodulation technique based on the application of a weak electrical current by means of a pair of electrodes placed in the head of the patient over target cortical areas. t-DCS is able to modulate the cortical activity by means of neuronal subthreshold current flows, and membrane polarizing effects[71,72]. In healthy conditions, the neuronal effect of t-DCS depends on the polarity of the stimulation: anodal stimulation depolarize the neuron membrane leading to an enhancement of cortical excitability, while cathodal stimulation inhibits the underlying cortex trough hyperpolarization of the cellular membrane[73–78].

t-DCS delivered over the primary motor cortex (M1) has been tested in several movement disorders (PD, parkinsonisms, dystonic syndromes, tremors, ataxia, and so on) with promising, although sometimes conflicting, results[79–81]. In PD, M1 stimulation may improve the parkinsonian symptoms trough at least two different mechanisms: 1) an increase in M1 excitability may compensate for the hypoactive pallido-thalamo-cortical network, and 2) a dopamine release in the basal ganglia trough potentiation of the glutamatergic cortico-striatal pathway[82–86].

t-DCS has never been tested in the management of PD patients with PS, although the central pathogenetic hypothesis, which suggests an imbalance between the left and right basal ganglia outputs, appears to be a reasonable substrate for this approach. Novel therapeutic options are required considering that PS management is challenging, there are no guidelines on the optimal treatment approach, and the benefits achieved with the available therapies fade away in less than 6 months[29].

AIM OF THE STUDY

In this randomized, sham controlled, study we aim to evaluate the efficacy of a bi-hemispheric transcranial direct current stimulation in add-on to a standardized in-hospital rehabilitation program in the management of Pisa syndrome in Parkinson's disease. The primary outcome of the study will be the comparison of the improvement of overall trunk posture (lateral trunk inclination + anterior trunk flexion) in upright standing position at the end of the rehabilitation between t-DCS and sham groups. As secondary outcomes, we will assess the effects of t-DCS on the trunk range of motion during dynamic tasks as well as on motor impairment, functional independence, and pain.

MATERIALS and METHODS

- *Study population*

Thirty patients affected by PD and PS were consecutively enrolled among those attending the Neurorehabilitation Department of the IRCCS Mondino Foundation (Pavia, Italy) between January 2019 and August 2020. Idiopathic PD was diagnosed according to the Movement Disorders Society clinical diagnostic criteria[87]. PS was clinically diagnosed according to the following criteria[21–23]:

- a lateral flexion of the trunk with a homogenous angle between sacrum and spinous process of the 7th cervical vertebra;
- an ipsilateral axial rotation of the trunk around the sagittal axis, that leads to a higher and anterior position of the shoulder contralateral to the side of trunk deviation;
- the worsening of the postural disorder during standing position, sitting position and gait;
- the improvement of the postural disorder in supine position.

Inclusion criteria were represented by:

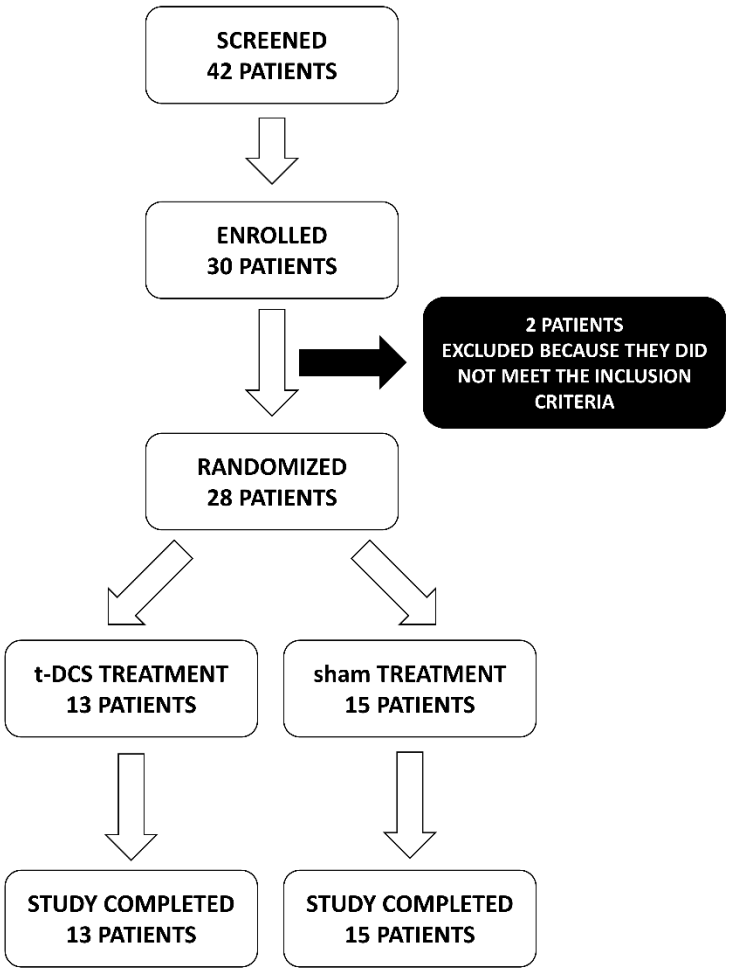
- age between 18 and 80 years;
- Hoehn and Yahr stage between II and III;
- Mini-Mental State Examination score above 24;
- lateral trunk flexion of at least 10° at baseline trunk kinematic analysis.

Exclusion criteria included:

- history of major psychiatric or other neurological conditions;
- history of back surgery, tumors or infections of the spine, intradural or extradural hematoma, ankylosing spondylitis, spinal stenosis;
- history of idiopathic scoliosis;
- botulin toxin treatment in the previous year;
- any change in dose or regimen of the anti-parkinsonian therapy in the last month before enrolment.

Two patients were screening failures because their lateral trunk flexion recorded at baseline was below 10°. The final study population consisted of 28 subjects (21 men, 72.9±5.1 years old) (Figure 2).

Figure 2 – Flow diagram of the progress through the phases of the study



Legend: t-DCS: transcranial direct current stimulation.

- *Study procedures*

The study was a randomized, double-blind, controlled trial aimed to assess the efficacy of five daily sessions of bi-hemispheric t-DCS in add-on to an in-hospital neurorehabilitation protocol in patients affected by PD and PS.

At hospital admission (T0 – baseline), all patients underwent complete neurological, general and functional examinations by a Neurologist with expertise in movement disorders and neurorehabilitation. Patients who fulfilled inclusion and exclusion criteria underwent a baseline trunk kinematic analysis. Patients with at least 10° of lateral trunk flexion completed the baseline evaluations with a dynamic EMG study of trunk muscles, and with administration of a set of clinical scales for the evaluations of motor impairment, functional independence, and lumbar pain.

After that, patients were randomly assigned to "t-DCS" or "sham" treatment, and they started the double-blind phase of the study. The 5-day t-DCS/sham treatment was delivered in 5 daily consecutive sessions, starting from the first Monday after hospital admission. In parallel to neuromodulation, all patients were treated with a standardized 4-week rehabilitation program. The kinematic analysis of trunk movement as well as the administration of the set of questionnaires were repeated at the end of the 4-week rehabilitation program (T1 - hospital discharge), and 6 months after discharge (T2) (Figure 3).

The randomization was performed according to a block randomization method. A unique randomization list was generated before enrollment with the following parameters: 6 blocks; 6 patients per block (3 for t-DCS group, and 3 for sham group).

All the patients were treated with an optimized and individualized anti-parkinsonian therapy, which dose and regimen were kept stable during the overall study period. All the evaluations were performed in the morning, and always in an ON phase.

The local ethics committee approved the study (p-20190052462), and all the participants signed a written informed consent before enrollment. The trial was registered at www.clinicaltrials.gov (NCT04620863). This study was funded by the Italian Ministry of Health ("Ricerca Corrente" 2018-2020). The study was completed in September 2020.

- *Transcranial direct current stimulation (t-DCS)*

Transcranial direct current stimulation (t-DCS) was delivered by an expert technician (V.G.) who was not otherwise involved in the management of the patients. The managing physician as well as the physiotherapist were blind to the type of stimulation.

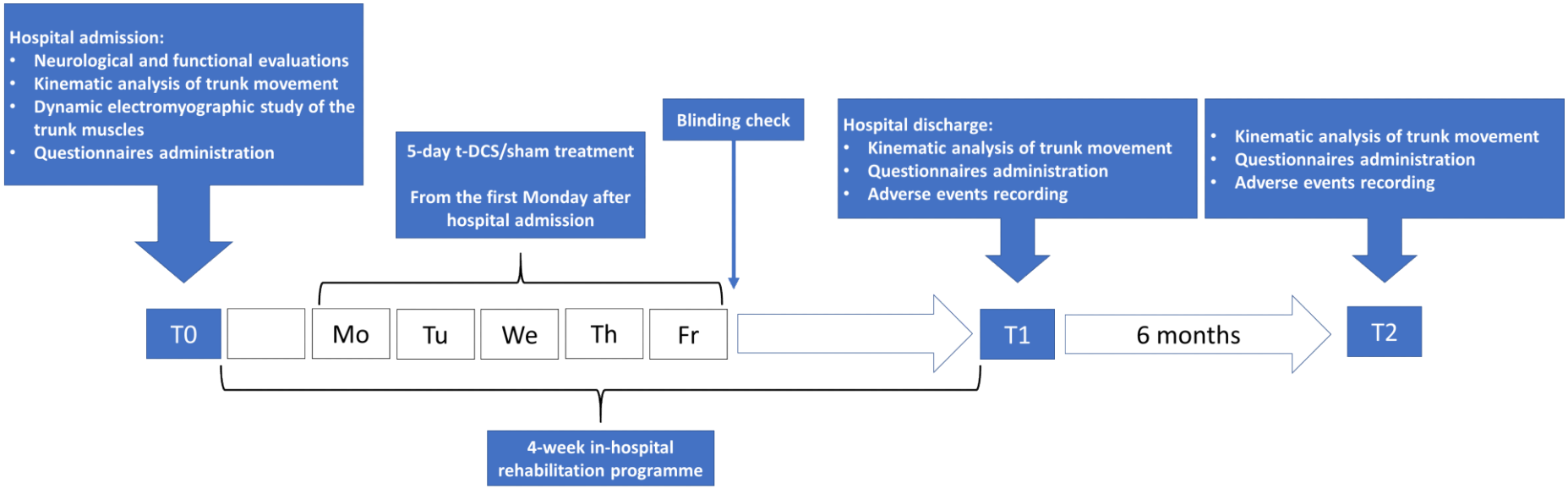
Neuromodulation was delivered via a specific battery-driven direct current stimulator (Newronika HDCstim, Newronika s.r.l.). The current was transferred by an approved saline-soaked pair of surface sponge electrodes (anode and cathode of 3x3 cm).

All the participants received daily stimulation sessions for 5 consecutive days, starting from the first Monday after hospital admission (Monday to Friday). The primary motor cortex (M1) was identified using the International 10-20 system for C3 (left M1) or C4 (right M1). For the stimulation, the anode was placed over the primary motor cortex (M1) ipsilateral to the side of trunk deviation, and the cathode was placed over the primary motor cortex (M1) contralateral to the side of trunk deviation (bi-hemispheric stimulation). This approach was decided according to previous positive data from literature, and to the pathogenetic central hypothesis of PS in PD[34,88,89].

Patients randomized to the t-DCS group were treated with the following parameters: duration of stimulation of 20 minutes per session with a 2 mA intensity delivered at anodal and cathodal levels.

In the sham group, patients underwent the same number of sessions that lasted 20 minutes, but the stimulation the stimulation setting was exactly the same but the stimulation intensity was set according to a ramping up/ramping down method and delivered only in the first and last 30 seconds of each session[78]. This stimulation paradigm is insufficient to produce a meaningful therapeutic effect, but it is necessary to guarantee the blind condition as it mimics the possible initial tingling sensation associated with active stimulation. All participants were informed about possible feelings related to the t-DCS treatment, such as a tingly sensation under the electrodes at the beginning of the stimulation. These procedures adequately blind participants to their group allocation[90,91]. At the end of the 5-day stimulation period, a blind check was performed by asking the patients if they believed they had received real or sham stimulation. All patients tolerated well the stimulation and no side effects occurred.

Figure 3 – Flowchart of study procedures



Legend: t-DCS: patients randomized to transcranial direct current stimulation (*n*=13). sham: patients randomized to sham stimulation (*n*=15).

- *In-hospital rehabilitation program*

All patients enrolled were treated with a specific and standardized in-hospital rehabilitation program which was focused on the rehabilitation of the trunk postural disorder[31,54]. According to the present regional law (n° X/ 1980, 20th June 2014), all patients were treated with 90-minute daily sessions, 6 days a week (Monday to Saturday) for four weeks.

Each session was structured as follow:

- 10 minutes of cardiovascular warm-up activities: intersegmental coordination exercises; exercises to release shoulder and pelvic girdle; pelvic anteversion and retroversion movements to improve diaphragmatic respiration (supine position); breathing exercises to promote expansion of the chest;
- 15 minutes of stretching exercises: exercises to stretch the muscles of the posterior kinematic chain; exercises to stretch the pectoralis muscles; exercises to stretch the ischio-cruralis muscles; assumption of the prone position, sitting on heels and stretching the arms out in front; the "bridge" exercise to stretch the muscles of the anterior abdominal wall, glutei, quadriceps and hamstring; exercises to stretch lumbar muscles (in the supine position, each knee, in turn, is brought to the chest);
- 15 minutes of strengthening exercises in a functional context: exercises to strengthen the dorsal muscles (arms extended and hands outstretched as though to take something); lateral bending (arms lying along the body and hands reaching down as though to pick up something); stretching using the wall bars;
- 20 minutes of gait training: overground gait training (forwards, backwards, and lateral); walking on the spot;
- 15 minutes of balance training: path with obstacles; balance exercises performed in order of difficulty (heel-to-toe walking, lateral walking crossing the legs, walking along a path on surfaces of different texture);
- 15 minutes of relaxation exercises: intersegmental coordination exercises; segmental passive mobilization (until maximum joint range of motion is reached); breathing exercises to promote expansion of the chest.

- *Kinematic analysis of trunk movement*

Kinematic analysis of trunk was performed with a 4-camera optoelectronic system (SMART DX 400, BTS Engineering, Milan, Italy) with a sampling rate of 100 Hz. Ten spherical reflective markers (15 mm in diameter) were applied at the following sites:

- right acromial process;
- left acromial process;
- spinous process of the 7th cervical vertebra (C7);
- spinous process of the 4th thoracic vertebra;
- spinous process of the 9th thoracic vertebra;
- spinous process of the 12th thoracic vertebra;
- spinous process of the 3rd lumbar vertebra;
- sacral prominence (Sa);
- right anterior-superior iliac spines (ASISr);
- left anterior-superior iliac spines (ASISl).

We studied the patients in static and dynamic conditions. Upright standing position was recorded with subjects standing with their feet 10 cm apart and their arms lying along their trunk. For the dynamic tasks, patients were asked to perform a lateral trunk bending (ipsilateral and contralateral to the side of trunk deviation), a forward trunk flexion and a posterior trunk extension. For each dynamic task they had to reach the maximal range of motion, starting from the upright standing position, and back. Each movement was repeated 4 times, and subjects were allowed to rest as needed between series. The average value of the 4 recordings was used for the analysis.

Synchronized acquisition and data processing were performed using the "SMART analyzer" software (BTS, Milan, Italy). As measurement of lateral and anterior trunk deviation, we considered the absolute deviation of the "C7-Sa" segment from the vector perpendicular to the floor of our movement analysis laboratory during static upright standing position. For the dynamic tasks, we calculated the range of motion (ROM) of trunk, defined as the maximum angle described by the C7-Sa segment starting from upright standing position to the end of each dynamic task.

C7-Sa deviation and ROMs were computed according to a previously validated two-landmark system[31,54]:

1) origin in Sa, X axis is the straight line passing in Sa and the middle point between ASISr and ASISl; Z axis is parallel to the bispinous-iliacae; Y axis is perpendicular to X and Z;
2) origin in Sa, Y axis tending from Sa to C7; X axis perpendicular to the plane made by Sa, C7 and T9; Z axis perpendicular to X and Y.

The following parameters were recorded and analyzed:
- Lateral trunk inclination in the upright standing position (Stat Bend);
- Anterior trunk flexion in the upright standing position (Stat Flex);
- Total postural alteration in the upright standing position (Stat Tot: Stat Bend + Stat Flex);
- ROM of trunk bending ipsilateral to the side of trunk deviation (ROM Ips);
- ROM of trunk bending contralateral to the side of trunk deviation (ROM Con);
- ROM of anterior trunk flexion (ROM Flex);
- ROM of posterior trunk extension (ROM Ext);
- Total ROM of the trunk (ROM Tot: ROM Ips + ROM Con + ROM Flex + ROM Ext);
- Total ROM of the trunk in the medio-lateral plane (ROM M-L: ROM Ips + ROM Con);
- Total ROM of the trunk in the antero-posterior plane (ROM A-P: ROM Flex + ROM Ext).

- *Questionnaires for motor impairment, functional independence, and lumbar pain*

PD related motor impairment was assessed trough the Unified Parkinson's Disease Rating Scale – part III – Motor examination (UPDRS-III)[92]. The item 3.13 Posture of the UPDRS-III scale was used as an overall measure of the postural alteration of PS in PD.

Finally, a motor asymmetry score (MAS) derived from the UPDRS-III score was calculated as previously defined by our group[26]. Briefly, for all the items that include a bilateral evaluation, the absolute value of the difference between the scores of right side and left side was calculated. The MAS is represented by the average of the difference of the single UPDRS-III items considered (namely: 3.3b-3.3c, 3.3d-3.3e, 3.4a-3.4b, 3.5a-3.5b, 3.6a-3.6b, 3.7a-3.7b, 3.8a-3.8b, 3.15a-3.15b, 3.16a-3.16b, 3.17a-3.17b, 3-17c-3.17d). Higher MASs are interpreted as high motor asymmetry between right and left sides, while low MASs are expression of low motor asymmetry.
Functional independence was measured trough the Functional Independence Measure (FIM)[93], while lumbar pain severity was rated according to a 0 to 10 visual analog scale (VAS).

- *Dynamic electromyographic (EMG) study of trunk muscles*

Before randomization, the patients underwent a dynamic EMG study of trunk muscles according to standardized procedures previously described by our group[26,31]. The EMG study was performed by two expert Neurophysiologists (E.A. and G.C.), not otherwise involved in the study procedures. In the present protocol, the aim of the EMG trunk analysis was to classify the muscles activation distribution of each patient according to the EMG patterns described by Tinazzi et al. (2013)[51]:

- Pattern I: hyperactivity of lumbar paraspinal ipsilateral to trunk leaning side, and:
  Subtype 1: associated to hyperactivity of thoracic paraspinal ipsilateral to trunk leaning side
  Subtype 2: associated to hyperactivity of thoracic paraspinal contralateral to trunk leaning side
- Pattern II: hyperactivity of lumbar and thoracic paraspinal contralateral to trunk leaning side, with hyperactivity of non-paraspinal muscles ipsilateral to trunk deviation (rectus femoris, iliopsoas, abdominal oblique).

The EMG analysis was performed bilaterally at the following levels: paraspinal lumbar muscles (L2-L4), paraspinal thoracic muscles (T8-T10), abdominal oblique muscles, iliopsoas, and rectus femoris.

The EMG study was performed with a Sinergy SYNC-5 (Viasys Healthcare, Manor Way, Old Woking, Surrey,UK). It was conducted by means of two hollow monopolar Teflon-coated needle electrodes. For each muscle, the reference electrode was applied 3 cm laterally to the needle. A ground electrode was applied at the shoulder level. Patients were tested in 4 different, static and dynamic, conditions: prone position, upright standing position, active right and left trunk bending. A given muscle qualified as “hyperactive” if it showed spontaneous and involuntary tonic EMG activity (longer than 500 ms according to data from literature) during a task normally characterized by EMG silence, in at least one of the four dynamic conditions previously described[26,31,42,51,94].

- *Statistical analysis*

The sample-size was calculated with the online platform www.openepi.com (Open Source Epidemiologic Statistics for Public Health). As primary outcome we considered the difference between t-DCS group and sham group in the Stat TOT at T1. According to previous data from literature and to our clinical experience, we considered as clinically meaningful a between groups difference in the Stat TOT percentage improvement of at least 15±10%. The computation was made with the following parameters: confidence interval (two-sided): 95%; power: 80%; ratio of sample-size: 1:1; mean difference: 15; standard deviation: 10. The minimum sample size suggested was of 24 patients (12 patients per group), drop-outs excluded.

The Statistical Package for the Social Sciences (SPSS), version 21.0 (Windows), was used for all the computations. The Kolmogorov-Smirnov test confirmed a normal distribution of our data. Continuous variables are presented as "mean±standard deviation", while categorical data are presented as "number (percentage)". For the statistical analysis, the data regarding the analysis of movement parameters as well as the scores of the administered questionnaires were normalized to a 100% baseline and expressed at T1 and T2 as percentage modifications.
Only for MAS the absolute values were used instead of the percentage variations, to allow a better interpretation.
At baseline, between groups comparison was performed with a Student's t-test for independent samples. Statistical association among categorical variables was tested with Pearson χ^2 test or Fisher exact test, if appropriate.
The main analysis was performed with ANOVA for repeated measures with two factors: TIME (3 levels: T0 vs. T1 vs. T2) and STIM (2 levels: t-DCS group vs. sham group), followed by a post-hoc Bonferroni's correction for intra-group comparisons.
A significant level of the described factors was interpreted as follow: a significant factor TIME was interpreted as an effect of the rehabilitation program independently from the t-DCS/sham treatment; a significant factor STIM was expression of a difference between t-DCS and sham groups, without difference in the persistence of the effect over time; a significant TIMExSTIM was interpreted as a difference between t-DCS and sham groups as well as a difference in the persistence of the effects between groups over time. Iif a significant interaction TIMExSTIM was found, a post-hoc analysis was separately performed for the t-DCS group and the sham group.
Finally, to rule out a significant association between the clinical and demographic features and the variables of outcome, we performed an ANOVA for repeated measures tests with factor

TIME, and factors: gender (male vs. female), type of PD at onset (tremor-dominant-type vs. akinetic-rigid-type vs. complete-type), most affected side of PD at onset (left vs. right vs. bilateral), side of trunk deviation (left vs. right), EMG pattern (I-1 vs. I-2 vs. II).

The level of significance was set at $\alpha=0.05$, always corrected for multiple comparisons where appropriate.

RESULTS

- *Clinical and demographic features of study population*

The t-DCS group (*n*=13, 9 males, 71.9±5.2 years old) and the sham group (*n*=15, 12 males, 73.7±5.0 years old) were comparable for clinical and demographic features (Table 1).

In the t-DCS group, PD duration was 8.7±5.8 years, the most affected side at onset was the left in 4 (30.8%) patients, the right in 5 (38.5%) patients, while it was symmetric in 4 (30.8%) patients. The type of PD at onset was tremor-dominant in 4 (30.8%) patients, akinetic-rigid in 8 (61.5%) patients, and complete in 1 (7.7%) patient. PS duration was 2.8±2.2 years, the trunk deviation was toward the left side in 7 (53.8%) of patients, and the EMG pattern was the I-1 in 6 (46.2%) patients, the I-2 in 3 (23.1%) patients, and the II in the remaining 4 (30.8%) patients (Figure 4).

In the sham group, PD duration was 9.8±8.8 years, the most affected side at onset was the left in 4 (26.7%) patients, and the right in 8 (53.3%) patients, while it was symmetric in 3 (20.0%) patients. The type of PD at onset was tremor-dominant in 3 (20.0%) patients, akinetic-rigid in 9 (60.0%) patients, and complete in 3 (20.0%) patients. PS duration was 3.1±1.7 years, the trunk deviation was toward the left side in 6 (40.0%) of patients, and the EMG pattern was the I-1 in 6 (40.0%) patients, the I-2 in 4 (26.7%) patients, and the II in the remaining 5 (33.3%) patients (Figure 4).

The EMG patterns were not associated to specific clinical and demographic features.

In the subset of patients with unilateral or asymmetric motor symptoms at PD onset (21 subjects, 9 in t-DCS group, and 12 in sham group), the side of PS trunk deviation was toward the most affected side in 9 (42.9%) patients, of which 5 (55.6%) in t-DCS, and 4 (33.3%) in sham group; (p=0.396).

- *Kinematic analysis of movement at baseline*

The postural alterations in upright standing position were comparable between t-DCS and sham groups at baseline (Stat Bend: p=0.732; Stat Flex: p=0.964; Stat Tot: p=0.920).

The ROM of trunk bending ipsilateral to the side of trunk deviation (ROM Ips: p=0.189), of anterior trunk flexion (ROM Flex: p=0.554), and of posterior trunk extension (ROM Ext: p=0.754) were comparable between t-DCS and sham groups as well. In contrast, the ROM of

trunk bending contralateral to the side of trunk deviation was lower in t-DCS group when compared to sham group (ROM Con: p=0.032).
The total ROM of the trunk (ROM Tot: p=0.179), ROM of the trunk in the medio-lateral plane (ROM M-L: p=0.523), and the ROM of the trunk in the antero-posterior plane (ROM A-P: p=0.122) were comparable between t-DCS and sham groups.
Data are summarized in Table 2.

- *Clinical scales at baseline*

At baseline, the two study groups showed similar levels of functional independence (FIM: p=0.061), motor impairment (UPDRS-III: p=0.520) and postural alteration as measured by the item 3.13 Posture of the UPDRS-III scale (p=0.790). The MAS was comparable between t-DCS and sham groups as well (p=0.467) (Table 3).

Lumbar pain was reported in 7 (53.8%) patients of the t-DCS group, and in 8 (53.3%) of the sham group (p=0.638). Pain severity was comparable between t-DCS and sham groups (VAS: p=0.758) (Table 3).

- *Blinding check*

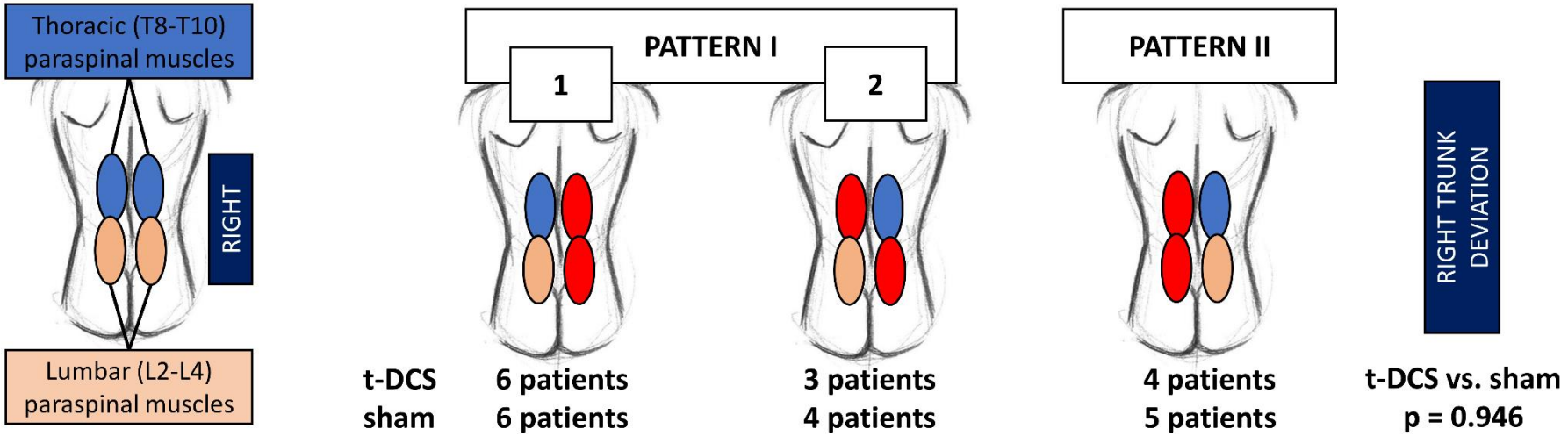
Seven out of 13 patients (53.8%) in the t-DCS group, and 8 out of 15 patients (53.3%) in the sham group declared they received active treatment (p=0.978).

Table 1 – Clinical and demographic features of study population

		All patients	t-DCS group	sham group	p-value
n		28	13	15	
Age (years)		72.9±5.1	71.9±5.2	73.7±5.0	0.377
Sex	Male	21 (75.0%)	9 (69.2%)	12 (80.0%)	0.512
	Female	7 (25.0%)	4 (30.8%)	1 (20.0%)	
PD duration (years)		9.3±7.4	8.7±5.8	9.8±8.8	0.702
Most affected side at PD onset	Left	8 (28.6%)	4 (30.8%)	4 (26.7%)	0.706
	Right	13 (46.4%)	5 (38.5%)	8 (53.3%)	
	Symmetric	7 (25.0%)	4 (30.8%)	3 (20.0%)	
Type of PD at onset	Tremor-dominant	7 (25.0%)	4 (30.8%)	3 (20.0%)	0.587
	Akinetic-rigid	17 (60.7%)	8 (61.5%)	9 (60.0%)	
	Complete	4 (14.3%)	1 (7.7%)	3 (20.0%)	
Ongoing anti-parkinsonian therapy	Levodopa	28 (100%)	12 (100%)	13 (100%)	-
	Dopamine agonist	22 (78.6%)	10 (76.9%)	12 (80.0%)	0.843
	COMT inhibition	16 (57.1%)	7 (53.8%)	9 (60.0%)	0.743
	MAO-B inhibition	9 (67.9%)	4 (30.8%)	5 (33.3%)	0.885
PS duration (years)		3.0±1.9	2.8±2.2	3.1±1.7	0.770
Side of trunk deviation	Left	13 (46.4%)	7 (53.8%)	6 (40.0%)	0.705
	Right	15 (53.6%)	6 (46.2%)	9 (60.0%)	
EMG pattern of trunk muscles activation	I-1	12 (42.9%)	6 (46.2%)	6 (40.0%)	0.946
	I-2	7 (25.0%)	3 (23.1%)	4 (26.7%)	
	II	9 (32.1%)	4 (30.8%)	5 (33.3%)	

Legend: PD: Parkinson's disease. PS: Pisa syndrome. t-DCS: patients randomized to transcranial direct current stimulation (*n*=13). sham: patients randomized to sham stimulation (n=15). COMT: catechol-O-methyltransferase. MAO-B: monoamine oxidase B. EMG pattern of trunk muscles activation: I-1: pattern I, subtype 1; I-2: pattern I, subtype 2, II: Pattern II; please see Tinazzi et al. 2013 and "dynamic EMG study of trunk muscles" paragraph for further details.

Figure 4 – Distribution of the electromyographic (EMG) pattern in t-DCS and sham groups



Legend: t-DCS: patients randomized to transcranial direct current stimulation (*n*=13). sham: patients randomized to sham stimulation (*n*=15). Red dots depict "hyperactive" muscles defined as presence of spontaneous and involuntary tonic EMG activity (longer than 500 ms) during a task normally characterized by EMG silence.

Table 2 – Baseline parameters of the kinematic analysis of trunk movement

	All patients	t-DCS group	sham group	p-value
n	28	13	15	-
Static upright standing position (degree)				
Stat Tot	41.9±18.7	42.3±16.6	41.5±20.9	0.920
Stat Bend	15.9±7.2	16.4±4.4	15.4±9.1	0.732
Stat Flex	25.9±13.3	25.8±13.5	26.1±13.5	0.964
Range of motion (ROM) of active dynamic tasks (degree)				
ROM Ips	19.2±10.1	16.5±5.9	21.5±12.3	0.189
ROM Con	18.4±6.6	15.5±6.1	20.8±6.3	0.032
ROM Flex	59.4±21.3	56.8±23.3	61.7±20.0	0.554
ROM Ext	14.3±6.2	13.9±6.4	14.7±6.1	0.754
ROM Tot	111.3±31.1	102.7±32.4	118.7±29.1	0.179
ROM M-L	37.6±13.6	32.0±8.3	42.4±15.6	0.042
ROM A-P	73.7±22.8	70.7±25.9	76.4±20.3	0.523

Legend: t-DCS: patients randomized to transcranial direct current stimulation (*n*=13). sham: patients randomized to sham stimulation (*n*=15). Stat Tot: Total postural alteration in the upright standing position. Stat Bend: Lateral trunk inclination in the upright standing position. Stat Flex: Anterior trunk flexion in the upright standing position. ROM: range of motion. ROM Ips: ROM of trunk bending ipsilateral to the side of trunk deviation. ROM Con: ROM of trunk bending contralateral to the side of trunk deviation. ROM Flex: ROM of anterior trunk flexion. ROM Ext: ROM of posterior trunk extension. ROM Tot: sum of trunk ROMs of the four dynamic tasks. ROM M-L: ROM of the trunk in the medio-lateral plane. ROM A-P: ROM of the trunk in the antero-posterior plane.

Table 3 – Baseline scores of administered clinical scales

	All patients	t-DCS group	sham group	p-value
n	28	13	15	-
UPDRS-III	30.6±8.8	29.5±10.1	31.7±7.7	0.520
Item 3.13 Posture of the UPDRS-III	2.6±0.8	2.6±0.9	2.5±0.7	0.790
MAS	0.42±0.3	0.46±0.3	0.39±0.2	0.467
FIM	93.8±15.9	87.8±15.3	99.0±14.9	0.061
Patients with lumbar pain	15 (53.6%)	7 (53.8%)	8 (53.3%)	0.638
VAS	3.3±3.2	3.5±3.4	3.1±3.3	0.758

Legend: t-DCS: patients randomized to transcranial direct current stimulation (*n*=13). sham: patients randomized to sham stimulation (*n*=15). UPDRS-III: Unified Parkinson's Disease Rating Scale – part III – Motor examination. MAS: motor asymmetry score (defined in the Materials and Methods section). FIM: Functional Independence Measure. VAS: 0 to 10 visual analog scale for lumbar pain severity.

- *Effects of t-DCS and sham treatments on the kinematic analysis of trunk parameters in upright standing position*

The total postural alteration in the upright standing position (Stat Tot – primary outcome) improved after rehabilitation in the overall study population (TIME: p=0.001). The improvement was more pronounced in the t-DCS group when compared to the sham group (STIM: p=0.014). At post-hoc intra-group analyses (TIMExSTIM: p=0.037), Stat Tot parameter was not modified in the sham group (p=0.140); in contrast, in the t-DCS group Stat Tot was reduced both at T1 (p=0.001 vs. T0) and at T2 (p=0.001 vs. T0) when compared to baseline (Figure 5 – Panel A).

The lateral trunk inclination in the upright standing position (Stat Bend) improved after the rehabilitation program in the overall study population (TIME: p=0.005). The reduction of Stat Bend was more pronounced in the t-DCS group when compared to the sham group (STIM: p=0.013). The post-hoc intra-group analysis (TIMExSTIM: p=0.036) showed that the Stat Bend parameter was not modified in the sham group (p=0.375); in contrast, in the t-DCS group the lateral trunk inclination was reduced at T1 (p=0.001 vs. T0), but the improvement was not retained at T2 (p=0.118 vs. T0) (Figure 5 – Panel B).

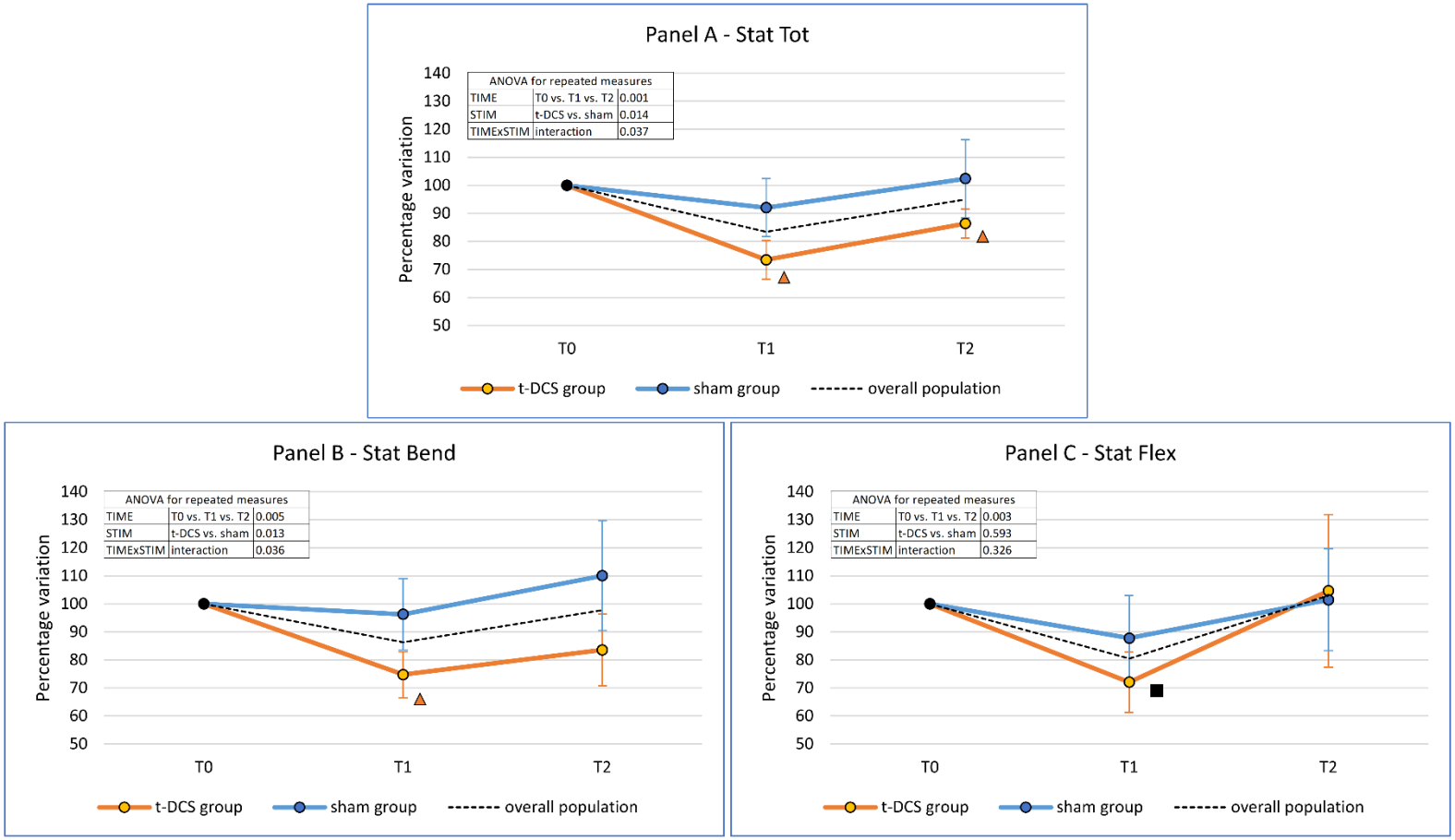
The anterior trunk flexion in the upright standing position (Stat Flex) improved significantly after rehabilitation in the overall study population (TIME: p=0.003), without differences between t-DCS and sham groups (STIM: p=0.593). When compared to T0, the Stat Flex improvement was significant at T1 (p=0.001 vs. T0), but not at T2 (p=0.223 vs. T0) in both groups (TIMExSTIM: p=0.326) (Figure 5 – Panel C).
Data presented are summarized in Table 4.

- *Effects of t-DCS and sham treatments on the kinematic analysis of trunk parameters during dynamic tasks*

The range of motion (ROM) of trunk bending ipsilateral to the side of trunk deviation (ROM Ips) increased after the rehabilitation program in the overall population (TIME: p=0.001). The improvement was higher in the t-DCS group when compared to the sham group (STIM: p=0.037). When compared to T0, the ROM Ips improvement was significant at T1 (p=0.001 vs. T0), but the improvement was not retained at T2 (p=0.079) in both groups (TIMExSTIM: p=0.089) (Figure 6 – Panel A).

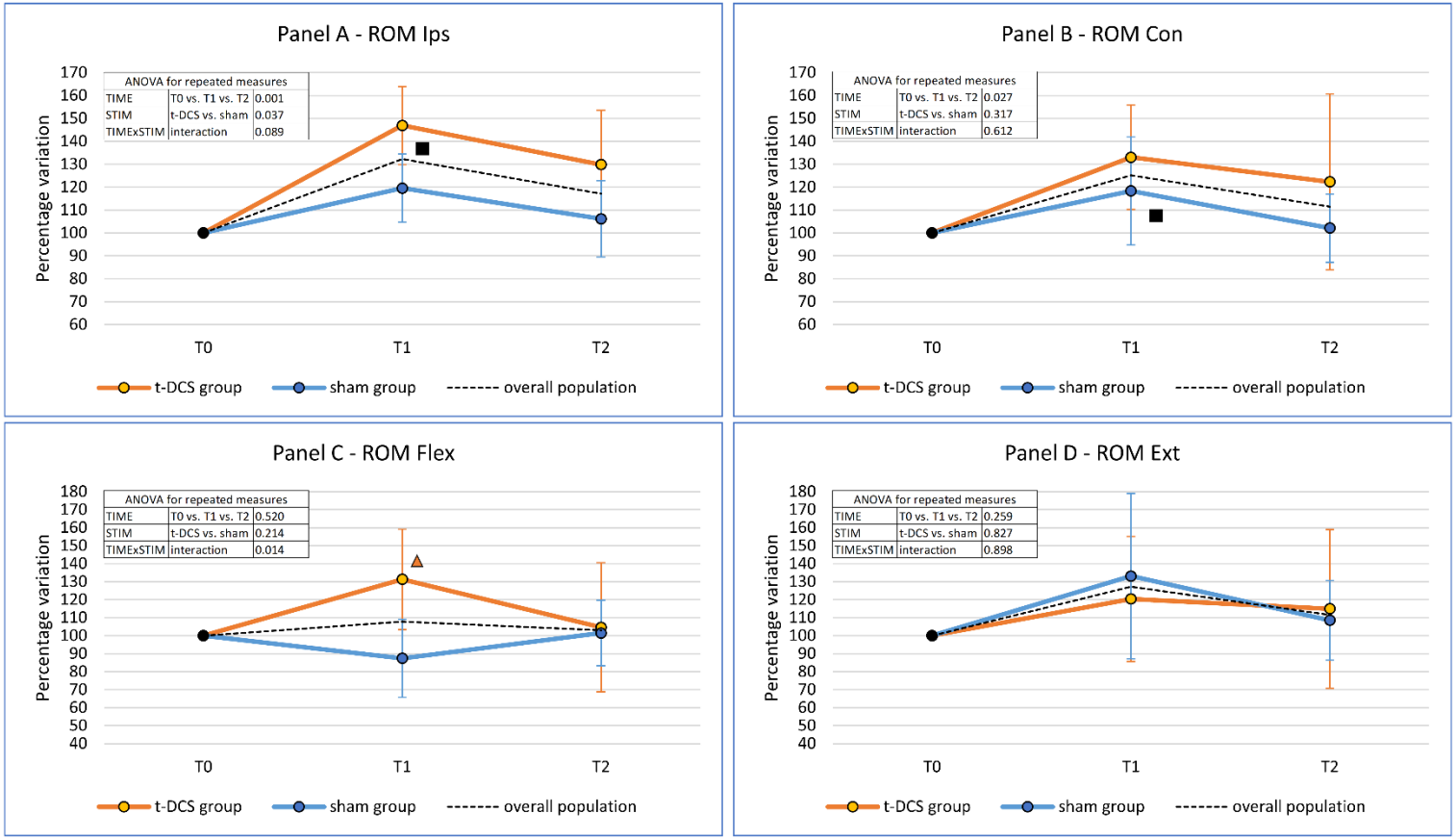
The ROM of trunk bending contralateral to the side of trunk deviation (ROM Con) increased after the rehabilitation program in the overall population (TIME: p=0.027), without significant differences between t-DCS and sham groups (STIM: p=0.317). When compared to T0, the ROM Con improvement was significant at T1 (p=0.022 vs. T0), but the improvement was not retained at T2 (p=0.791) in both groups (TIMExSTIM: p=0.612) (Figure 6 – Panel B).
Regarding the ROM of anterior trunk flexion (ROM Flex), we found a clearly separated behavior between t-DCS and sham groups (TIMExSTIM: p=0.014, TIME: p=0.520, and STIM: p=0.214). In particular, in t-DCS group we recorded an increase of ROM Flex at T1 (p=0.029 vs. T0) which did not persist at T2 (p=1.000 vs. T0). In contrast we did not detect significant changes in ROM Flex in the sham group (p=0.350) (Figure 6 – Panel C).
The ROM of posterior trunk extension (ROM Ext) was not modified at follow-up evaluations (TIME: p=0.259), and we did not find differences between t-DCS and sham groups (STIM: p=0.827, and TIMExSTIM: p=0.898) (Figure 6 – Panel D).
Data presented are summarized in Table 4.

Figure 5 – Effects of t-DCS and sham treatments on trunk deviation in upright standing position



Legend: t-DCS: patients randomized to transcranial direct current stimulation (*n*=13). sham: patients randomized to sham stimulation (*n*=15). Panel A - Stat Tot: total postural alteration in the upright standing position. Panel B - Stat Bend: lateral trunk inclination in the upright standing position. Panel C - Stat Flex: anterior trunk flexion in the upright standing position. *ANOVA for repeated measures:* factor "TIME" is expression of the efficacy of the rehabilitative treatment in the overall population; factor "STIM" is expression of the comparison between t-DCS and sham groups across all time-points. If the "TIMExSTIM" interaction was not significant, a post-hoc analysis was performed in the overall population: ■ = time-point vs. T0: $p<0.050$; in case of a significant "TIMExSTIM" interaction, a post-hoc analysis was separately performed for the t-DCS group and the sham group: Δ = time-point vs. T0: $p<0.050$ (the color identifies the group).

Figure 6 – Effects of t-DCS and sham treatments on trunk mobility during active dynamic tasks



Legend: t-DCS: patients randomized to transcranial direct current stimulation (n=13). sham: patients randomized to sham stimulation (n=15). ROM: range of motion. Panel A - ROM Ips: ROM of trunk bending ipsilateral to the side of trunk deviation. Panel B - ROM Con: ROM of trunk bending contralateral to the side of trunk deviation. Panel C - ROM Flex: ROM of anterior trunk flexion. Panel D - ROM Ext: ROM of posterior trunk extension. *ANOVA for repeated measures:* factor "TIME" is expression of the efficacy of the rehabilitative treatment in the overall population; factor "STIM" is expression of the comparison between t-DCS and sham groups across all time-points. If the "TIMExSTIM" interaction was not significant, a post-hoc analysis was performed in the overall population: ■ = time-point vs. T0: $p<0.050$; in case of a significant "TIMExSTIM" interaction, a post-hoc analysis was separately performed for the t-DCS group and the sham group: Δ = time-point vs. T0: $p<0.050$ (the color identifies the group).

- *Effects of t-DCS and sham treatments on the kinematic analysis parameters representative of global trunk mobility*

The total ROM of the trunk during the four dynamic tasks (ROM Tot) significantly increased in the overall study population (TIME: p=0.001). A different behavior over time was described between t-DCS and sham groups (TIMExSTIM: p=0.012, STIM: p=0.160). Specifically, in the t-DCS group we found an improvement at T1 (p=0.003 vs. T0), which was not retained at T2 (p=1.000 vs. T0), while no improvement was detected in the sham group (p=0.331) (Figure 7 – Panel A).

The ROM of the trunk in the medio-lateral plane (ROM M-L) increased after the rehabilitation program in the overall population (TIME: p=0.001). The improvement was more pronounced in the t-DCS group when compared to the sham group (STIM: p=0.034). When compared to T0, the ROM M-L improvement was significant at T1 (p=0.001 vs. T0), but it was not retained at T2 (p=0.071) in both groups (TIMExSTIM: p=0.104) (Figure 7 – Panel B).
Regarding the ROM of the trunk in the antero-posterior plane (ROM A-P), we did not find modifications over time (TIME: p=0.935), or differences between t-DCS and sham groups (p=0.268). Moreover, although a borderline significance was found for the TIMExSTIM interaction (p=0.047), the post-hoc analyses did not show significant changes of ROM A-P in the t-DCS group (p=0.080), or sham group (p=0.384) (Figure 7 – Panel C).
Data presented are summarized in Table 4.

- *Effects of t-DCS and sham treatments on motor impairment, postural score, and motor asymmetry score*

Motor impairment, as measured by UPDRS-III score, was reduced at T1 (p=0.001 vs. T0) but not at T2 (p=0.056 vs. T0) in the overall population (TIME: p=0.001), without differences between t-DCS and sham groups (STIM: p=0.942, and TIMExSTIM: p=0.836) (Figure 8 – Panel A) (Table 5).

When the posture-specific item 3.13 of UPDRS-III was separately analyzed, we found a clear distinction between t-DCS and sham groups (TIMExSTIM: p=0.001, STIM: p=0.001, and TIME: p=0.001). In particular, item 3.13 score was unchanged in the sham group (p=0.202), while it improved at T1 (p=0.001 vs. T0), and T2 (p=0.001 vs. T0) in the t-DCS group (Figure 8 – Panel B) (Table 5).

The motor asymmetry score (MAS) significantly improved in the overall study population (TIME: p=0.002). A different behavior over time was described between t-DCS and sham groups (TIMExSTIM: p=0.029, STIM: p=0.527). At post-hoc analyses, in the t-DCS group we described a MAS reduction at T2 (p=0.026 vs. T0). In contrast, no modifications of MAS were described in the sham group (p=0.566) (Figure 8 – Panel C).

- *Effects of t-DCS and sham treatments on functional independence, and prevalence and severity of lumbar pain*

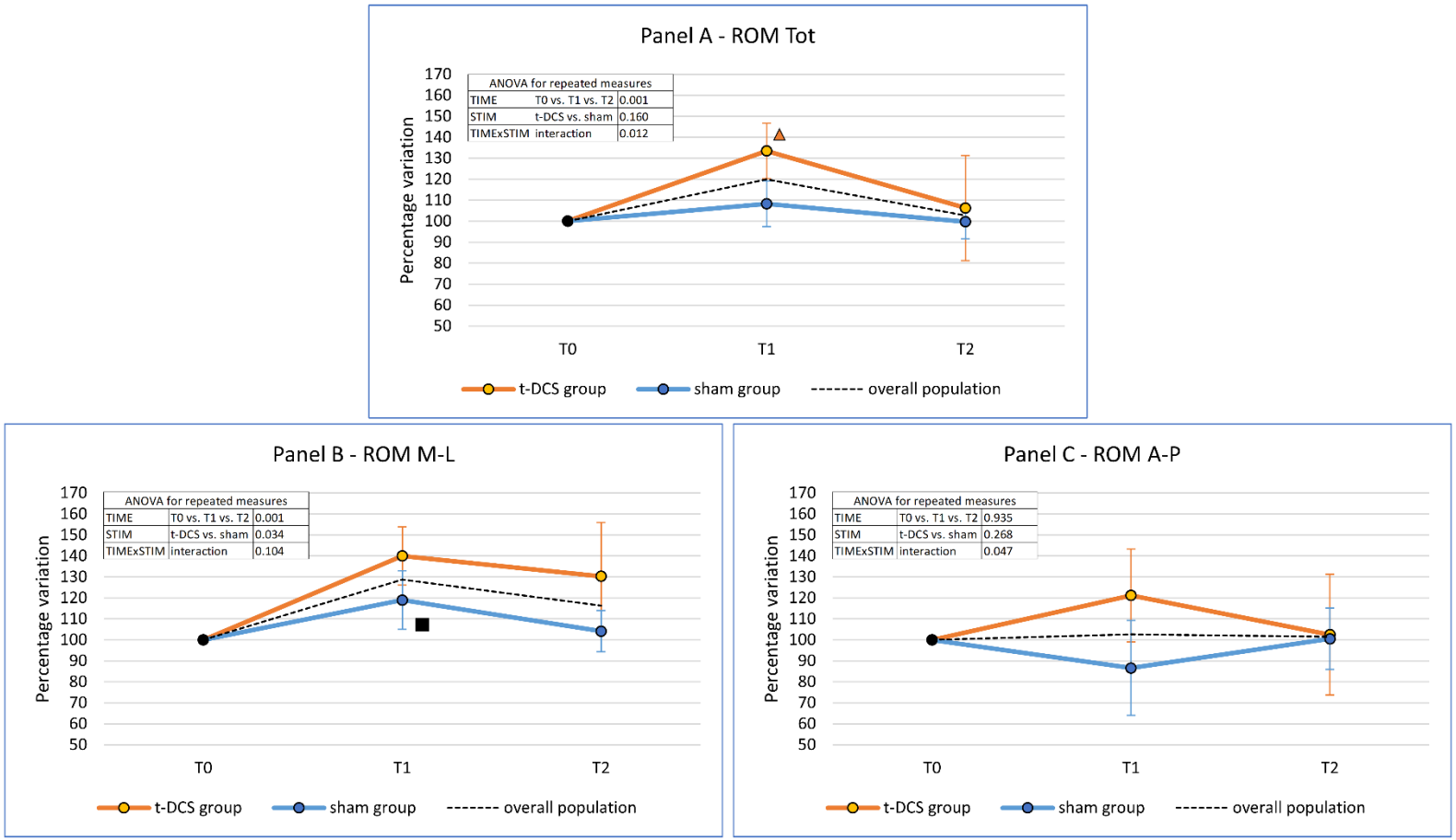
The functional independence, as measured by FIM score, improved after rehabilitation in both groups (TIME: p=0.001). The increase in FIM score was greater in the t-DCS group when compared to the sham group (STIM: p=0.048). The improvement duration was comparable in both groups (TIMExSTIM: p=0.095), and it was significant at T1 (p=0.001 vs. T0), and T2 (p=0.025 vs. T0) (Figure 9 – Panel A) (Table 5).

The percentage of patients affected by lumbar pain was comparable between t-DCS and sham groups at T1 (p=0.500) and T2 (p=0.604). The overall percentage of patients with lumbar pain did not change throughout the study evaluations (p=0.105) (Figure 9 – Panel B).
Fourteen patients (7 in both groups) reported lumbar pain at all time-points. In this subgroup of patients, lumbar pain improved in the overall population after the rehabilitation program (TIME: p=0.001). The improvement in pain scores was more pronounced in the t-DCS group when compared to the sham group (STIM: p=0.017). Moreover, the persistence of VAS reduction was different between t-DCS and sham groups (TIMExSTIM: p=0.035). In the sham group, the lumbar pain improvement was significant at T1 (p=0.049 vs. T0), but the improvement was not retained at T2 (p=0.583 vs. T0). In contrast, in the t-DCS group, lumbar pain score was significantly lower both at T1 (p=0.001 vs. T0) and T2 (p=0.001 vs. T0) (Figure 9 – Panel C) (Table 5).

- *Effects of clinical and demographic variables on primary and secondary outcomes*

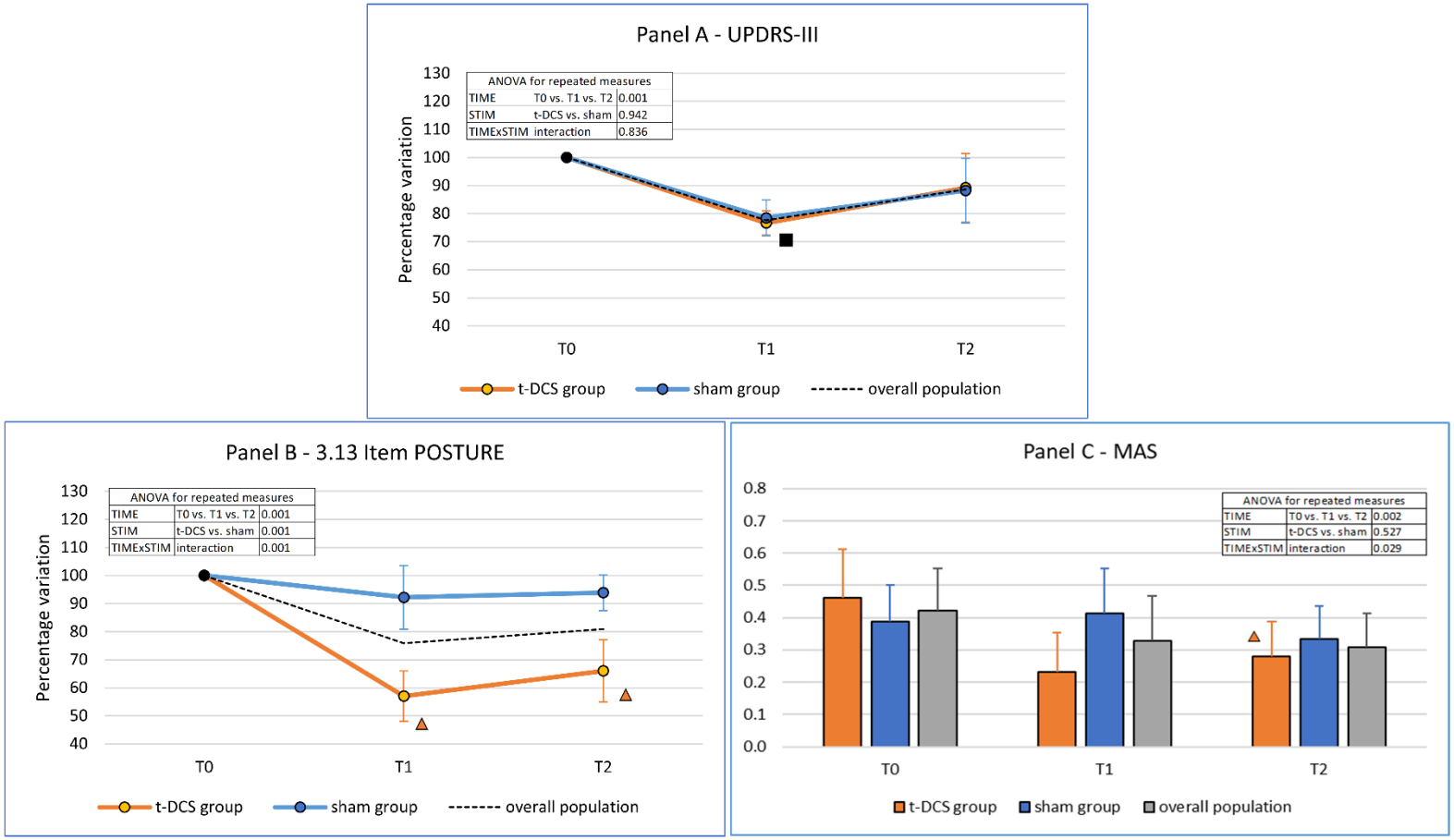
The kinematic analysis of trunk parameters as well as the scores of the administered questionnaires were not influenced by gender (male vs. female), type of PD at onset (tremor-dominant-type vs. akinetic-rigid-type vs. complete-type), most affected side of PD at onset (left vs. right vs. bilateral), side of trunk deviation (left vs. right), or EMG pattern (I-1 vs. I-2 vs. II).

Figure 7 – Effects of t-DCS and sham treatments on parameters of global trunk mobility



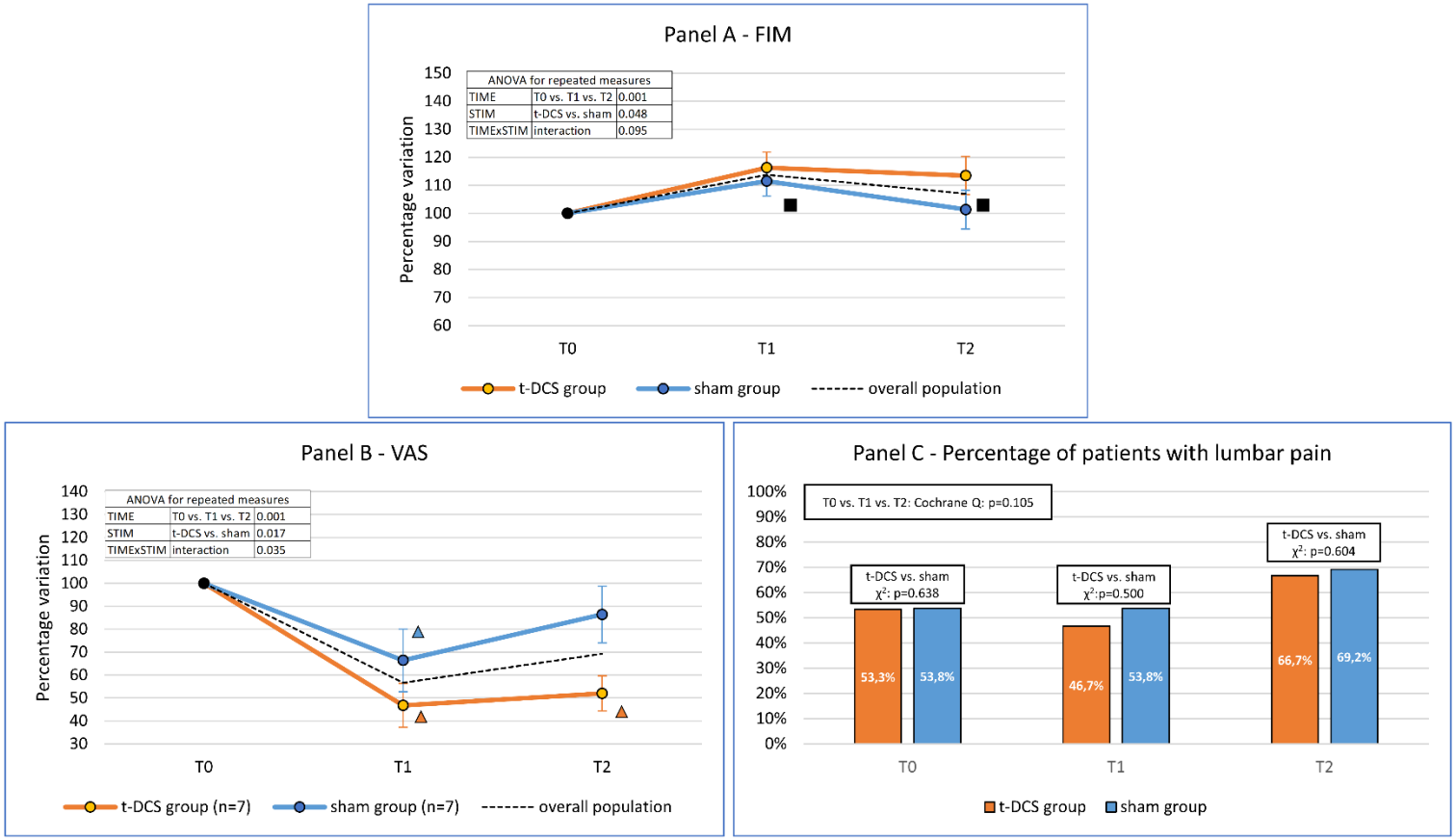
Legend: t-DCS: patients randomized to transcranial direct current stimulation (*n*=13). sham: patients randomized to sham stimulation (*n*=15). ROM: range of motion. Panel A - ROM Tot: sum of trunk ROMs of the four dynamic tasks. Panel B - ROM M-L: ROM of the trunk in the medio-lateral plane. Panel C - ROM A-P: ROM of the trunk in the antero-posterior plane. *ANOVA for repeated measures:* factor "TIME" is expression of the efficacy of the rehabilitative treatment in the overall population; factor "STIM" is expression of the comparison between t-DCS and sham groups across all time-points. If the "TIMExSTIM" interaction was not significant, a post-hoc analysis was performed in the overall population: ■ = time-point vs. T0: $p<0.050$; in case of a significant "TIMExSTIM" interaction, a post-hoc analysis was separately performed for the t-DCS group and the sham group: Δ = time-point vs. T0: $p<0.050$ (the color identifies the group).

Figure 8 – Effects of t-DCS and sham treatments on motor impairment, postural score and motor asymmetry score



Legend: t-DCS: patients randomized to transcranial direct current stimulation (*n*=13). sham: patients randomized to sham stimulation (*n*=15). Panel A - UPDRS-III: Unified Parkinson's Disease Rating Scale – part III – Motor examination. Panel B – Item 3.13 "Posture" of the UPDRS-III. Panel C - MAS: motor asymmetry score (defined in the Materials and Methods section). *ANOVA for repeated measures:* factor "TIME" is expression of the efficacy of the rehabilitative treatment in the overall population; factor "STIM" is expression of the comparison between t-DCS and sham groups across all time-points. If the "TIMExSTIM" interaction was not significant, a post-hoc analysis was performed in the overall population: ■ = time-point vs. T0: $p<0.050$; in case of a significant "TIMExSTIM" interaction, a post-hoc analysis was separately performed for the t-DCS group and the sham group: Δ = time-point vs. T0: $p<0.050$ (the color identifies the group).

Figure 9 – Effects of t-DCS and sham treatments on functional independence, and prevalence and severity of lumbar pain



Legend: t-DCS: patients randomized to transcranial direct current stimulation (*n*=13 in Panels A and C, *n*=7 in Panel B). sham: patients randomized to sham stimulation (*n*=15 in Panels A and C, *n*=7 in Panel B). Panel A - FIM: Functional Independence Measure. Panel B: VAS: 0 to 10 visual analog scale for lumbar pain severity; please note that only patients with persistent pain across all time points were considered. Panel C – prevalence of lumbar pain. *ANOVA for repeated measures:* factor "TIME" is expression of the efficacy of the rehabilitative treatment in the overall population; factor "STIM" is expression of the comparison between t-DCS and sham groups across all time-points. If the "TIMExSTIM" interaction was not significant, a post-hoc analysis was performed in the overall population: ■ = time-point vs. T0: $p<0.050$; in case of a significant "TIMExSTIM" interaction, a post-hoc analysis was separately performed for the t-DCS group and the sham group: Δ = time-point vs. T0: $p<0.050$ (the color identifies the group).

Table 4 – Percentage modifications of kinematic analysis of trunk movement parameters during study periods

	T0	T1			T2			ANOVA for repeated measures		
		All patients	t-DCS	sham	All patients	t-DCS	sham	TIME	STIM	TIMExSTIM
n	28	28	13	15	28	13	15			
Static upright standing position										
Stat Tot (%)	100	83.4±9.9	73.4±6.9	92.0±10.3	94.9±11.4	86.4±5.2	102.4±13.9	0.001	0.014	0.037
Stat Bend (%)	100	86.3±11.9	74.8±8.2	96.3±12.7	97.8±17.8	83.6±12.8	110.0±19.6	0.005	0.013	0.036
Stat Flex (%)	100	80.5±13.7	72.1±10.8	87.8±15.2	102.9±27.2	104.7±27.2	101.5±18.2	0.003	0.593	0.326
Range of motion (ROM) of active dynamic tasks										
ROM Ips (%)	100	132.3±17.1	147.0±17.0	119.6±14.9	117.2±20.7	129.8±23.6	106.2±16.7	0.001	0.037	0.089
ROM Con (%)	100	125.2±23.2	133.0±22.9	118.4±23.7	111.5±28.2	122.3±38.3	102.1±14.9	0.027	0.317	0.612
ROM Flex (%)	100	107.8±26.7	131.3±27.8	87.4±21.7	102.9±27.2	104.7±35.8	101.5±18.2	0,520	0.214	0.014
ROM Ext (%)	100	127.2±40.5	120.4±34.7	133.1±45.9	111.5±33.4	114.9±44.0	108.5±22.1	0.259	0.827	0.898
ROM Tot (%)	100	120.0±13.4	133.5±13.2	108.3±10.9	102.8±17.8	106.3±25.1	99.7±8.2	0.001	0.160	0.012
ROM M-L (%)	100	128.7±14.7	140.0±13.8	119.0±14.0	116.3±19.7	130.3±25.7	104.2±0.8	0.001	0.034	0.104
ROM A-P (%)	100	102.7±23.7	121.2±22.2	86.8±22.6	101.4±21.8	102.5±28.7	100.5±14.6	0.935	0.268	0.047

Legend: t-DCS: patients randomized to transcranial direct current stimulation (*n*=13). sham: patients randomized to sham stimulation (*n*=15). Stat Tot: Total postural alteration in the upright standing position. Stat Bend: Lateral trunk inclination in the upright standing position. Stat Flex: Anterior trunk flexion in the upright standing position. ROM: range of motion. ROM Ips: ROM of trunk bending ipsilateral to the side of trunk deviation. ROM Con: ROM of trunk bending contralateral to the side of trunk deviation. ROM Flex: ROM of anterior trunk flexion. ROM Ext: ROM of posterior trunk extension. ROM Tot: sum of trunk ROMs of the four dynamic tasks. ROM M-L: ROM of the trunk in the medio-lateral plane. ROM A-P: ROM of the trunk in the antero-posterior plane. *ANOVA for repeated measures:* factor "TIME" is expression of the efficacy of the rehabilitative treatment in the overall population; factor "STIM" is expression of the comparison between t-DCS and sham groups across all time-points; a significant TIMExSTIM interaction is expression of a difference between t-DCS and sham groups as well as difference in the persistence of the effects between t-DCS and sham groups over time.

Table 5 – Percentage modifications of clinical scale scores during study periods

	T0	T1			T2			ANOVA for repeated measures		
		All patients	t-DCS	sham	All patients	t-DCS	sham	TIME	STIM	TIMExSTIM
n	28	28	13	15	28	13	15			
UPDRS-III (%)	100	77.6±5.4	76.6±4.3	78.5±6.4	88.7±11.7	89.2±12.3	88.2±11.5	0.001	0.942	0.836
Item 3.13 Posture of the UPDRS-III (%)	100	75.9±13.5	57.1±11.1	92.2±11.3	81.0±11.2	66.0±11.1	93.9±6.4	0.001	0.001	0.001
FIM (%)	100	113.8±5.5	116.3±5.6	111.5±5.3	107.0±7.4	113.5±6.8	101.4±6.9	0.001	0.048	0.095
VAS (%) *	100	56.6±12.4	46.8±9.6	66.4±13.6	69.2±13.3	52.0±7.7	86.4±12.3	0.001	0.017	0.035

Legend: t-DCS: patients randomized to transcranial direct current stimulation (*n*=13). sham: patients randomized to sham stimulation (*n*=15). *Please note that for VAS analysis only patients with persistent pain across all time points were considered (*n*=14, *n*=7 in t-DCS group, and *n*07 in sham group). UPDRS-III: Unified Parkinson's Disease Rating Scale – part III – Motor examination. FIM: Functional Independence Measure. VAS: 0 to 10 visual analog scale for lumbar pain severity. *ANOVA for repeated measures:* factor "TIME" is expression of the efficacy of the rehabilitative treatment in the overall population; factor "STIM" is expression of the comparison between t-DCS and sham groups across all time-points; a significant TIMExSTIM interaction is expression of a difference between t-DCS and sham groups as well as difference in the persistence of the effects between t-DCS and sham groups over time.

DISCUSSION

Pisa syndrome is a frequent postural complication of PD, leading to higher motor impairment and functional disability, gait impairment, incidence of falls, lumbar pain, cognitive impairment, and mortality[1–3,23,31,95,96]. The management of PS in PD is still a challenge for the clinicians since no guidelines are available, the therapeutic options are limited, and the efficacy is short lasting[29]. Indeed, neurorehabilitation and botulinum toxin (BTx-A) represent the first line treatments, but the postural improvement lasts 6 months or less[31,52,54,55]. Deep Brain Stimulation seems to exert positive effects in PS, but its invasiveness and the lack of specifically designed clinical trial limit its application in clinical practice[61,64].

t-DCS is a non-invasive and manageable neuromodulation technique widely tested in movement disorders, such as Parkinson's disease and dystonia[79–81].

In this randomized, sham controlled, study we evaluated the effects of a bi-hemispheric transcranial direct current stimulation in add-on to a standardized 4-week hospital rehabilitation program in the management of PS in PD. The t-DCS stimulation paradigm consisted in a cathodal/inhibitory stimulation over the primary motor cortex (M1) contralateral to the side of trunk deviation, associated to an anodal/excitatory M1 stimulation ipsilateral to the side of PS (side of the more denervated striatum)[34,76].

This stimulation paradigm was based on previous reports provided by the groups of Furuya et al. and Rosset-Llobet et al. about the efficacy of bi-hemispheric t-DCS in focal dystonia[88,89,97]. Although PS is no longer included in pure trunk dystonia, it is quite surprisingly that t-DCS has never been tested in the management of PS in PD. Indeed, the hypothesized role of basal ganglia outputs asymmetry in PS appears to be a good substrate for the proposed bi-hemispheric approach[34]. It is worth noting, that this approach could also exert a positive effect on the interhemispheric/transcallosal imbalance that has been previously demonstrated in PD[98].

All patients were studied with kinematic analysis of movement in static (upright standing position), and dynamic (lateral bending, anterior flexion and trunk extension) conditions at baseline (T0), the end of the rehabilitation period (T1), and 6 months later (T2).

The results of the present study may be summarized as follows. The overall postural alteration in upright standing position improved with neurorehabilitation, and this improvement was more pronounced and persistent over time in the t-DCS group. The reduction in lateral trunk inclination was more conspicuous in the t-DCS group, while the reduction in anterior trunk flexion was comparable between t-DCS and sham groups.

The increase in the global range of motion (ROM) of the trunk was more pronounced in the t-DCS group, although this result was not maintained to T2. When the single dynamic tasks were analyzed separately, patients treated with t-DCS achieved better results in the ROM of trunk bending ipsilateral to the side of trunk deviation when compared to sham group, while the trunk bending contralateral to the side of PS improved as well after neurorehabilitation, without differences between t-DCS and sham groups.

The ROM of anterior trunk flexion increased only in the t-DCS group at T1, while trunk extension was not modified.

In line with previous results, the ROM of the trunk in the medio-lateral plane increased the most in the t-DCS group, while the ROM in the antero-posterior plane was not modified over time. All the described improvements in the dynamic tasks were reached at the end of the rehabilitation program, but they were not retained at 6 months.

The postural and mobility trunk improvement was coupled with a reduction of UPDRS-III score at T1 (comparable between t-DCS and sham groups) and a reduction of the posture specific 3.13 item of UPDRS-III at T1 and T2, which was greater in the t-DCS group. Moreover, the left to right asymmetry of the parkinsonian motor symptoms was reduced at T2 in the t-DCS group.

The increase in FIM score was significant at T1 as well as at T2 in the overall population, being more pronounced in the t-DCS group. Although the percentage of patients reporting lumbar pain was not reduced during the study, pain severity in patients with persistent pain across all time points (n=14) was lower in the t-DCS group; moreover, the reduction of pain was still present at 6 months only in the t-DCS group.

In line with previous data from literature, a major finding of the present study is the confirmation of the pivotal role of neurorehabilitation in the management of PS and PD[53–55,57,99,100]. Regardless of the active or sham treatment, the statistical analysis demonstrated a positive effect of the neurorehabilitation program on posture in upright standing position, on the global ROM of trunk as well as on the ROM of trunk bending and anterior trunk flexion, on motor impairment, functional independence and pain.

Expanding on these findings, t-DCS potentiates the effects of neurorehabilitation leading to better results on the lateral trunk flexion and the overall postural alteration in upright standing position as well as on the global ROM of the trunk, on the ROM of the trunk in the medio-lateral plane, on the ROM of trunk bending ipsilateral to PS, and on functional independence and pain. Moreover, in the t-DCS group, the effects of neurorehabilitation were more persistent,

and the overall static postural improvement, the increase of functional independence, and the pain reduction were retained at 6 months from hospital discharge.

Only six studies were specifically designed to test the efficacy of non-invasive therapies (neurorehabilitation, BTx-A or lidocaine injections) in patients with PS and PD[28,31,52,54,56,68], and among these only two were randomized controlled trials[28,31]. Three studies used a kinematic analysis of movement for recording the outcome measures[31,54,68], but only two of them evaluated trunk ROM during dynamic tasks[31,54]. In the remaining three studies, only the lateral trunk inclination was calculated by means of a wall goniometer[28,52,56].

The improvement achieved in our t-DCS group is consistent with previous data reporting a reduction between 30% and 50% of lateral trunk inclination as well as a comparable increase of ROMs of trunk flexion and bending[28,31,52,54,56,68]. In contrast with previous data, in patients treated with t-DCS in add-on to neurorehabilitation, the overall improvement of trunk posture and mobility persisted until 6 months. This result has a great clinical significance because the persistence of the improvement is one of the critical issues in the management of PS in PD.

Among the possible explanations, a better quality of rehabilitation because of reduced severity of PS as well as pain reduction during rehabilitation may be considered possible reasons for leading to longer lasting effects.

These suggested explanations are intriguing, as we know the pivotal role of neurorehabilitation in PD, and how anodal t-DCS of primary motor cortex itself proved effective across several pain conditions[53,86,101]. Moreover, even if the rehabilitation program was standardized, we are aware that physiotherapy relies on the motivation, compliance, and engagement of the patient.

A comparison with a previous report by our group on the efficacy of BTx-A in PS in PD may provide additional clues on the possible role of pain reduction[31]. Indeed, BTx-A proved effective in several pain conditions (chronic migraine, trigeminal neuralgia, neuropathic pain, orthopedic diseases and others)[102]. In our previous paper the patient group treated with BTx-A achieved better results in the postural disorder as well as in pain relief at the end of the 4-week rehabilitation when compared to placebo, which resembles the outcome of the present study. At variance from the present findings, the postural improvement as well as the reduction in pain score were not coupled with a significant retention of the clinical amelioration at 6 months in the botulinum study. This complicated picture makes it difficult to disentangle the effect of the intervention adopted (t-DCS or BTx-A) on pain from that on postural alignment. Therefore, we do not feel confident to sustain the hypothesis that the quality of rehabilitation treatment or the more pronounced pain relief may have played a major role in the long-term retention of the clinical improvement recorded in t-DCS group.

An alternative explanation is that t-DCS facilitates brain plasticity and motor learning, leading to a better and long-lasting retention of the rehabilitation treatment[103].
In this frame, it is tempting to hypothesize that the benefit may be extended over time by the possibility of repeating the t-DCS stimulation program, also in the ambulatory setting, and associated it to a tailored physical exercise program at home. Of course, future studies are needed to verify this hypothesis.
The improvement of the postural disorders may lead further benefits to the patients. PS is very eye-catching from an aesthetic point of view, and often the patients are so embarrassed in front of other people that they prefer social retirement for this reason more than for PD itself. A reduction of lateral trunk bending, and associated pain, may therefore increase the social interaction, and reduce inactivity.

Our data confirms that in the majority of the patients the side of trunk deviation was toward the less affected side of PD (12 out of 21 PD patients with clear asymmetric parkinsonian symptom at onset). After the randomization process, in 5 out of 8 (55.6%) PD patients enrolled in t-DCS group, the side of PS was toward the most affected side of PD at onset. This observation might have raised some concerns, because in this subgroup of patients we delivered a cathodal/inhibitory stimulation over the side of the most denervated striatum, possibly leading to a worsening of the parkinsonian symptoms. Our findings suggest that this was not the case, since motor impairment and functional independence improved in general and, more importantly, in the t-DCS group.
These results may be explained as follows. Considering that PS is associated with a higher UPDRS-III score of upper limb function, gait and postural instability[23,32,33], it is conceivable that the improvement of the postural disorder exerts a positive effect also on the associated parkinsonian symptoms. In this view, the improvement of PS seems to have a much more important clinical impact on motor impairment than the possible inhibitory effects of the cathodal stimulation.
BTx-A proved effective in PS in PD, but a subset of patients may not benefit from this treatment, namely those without a clear dystonia-like EMG pattern, those with a prevalent compensatory paraspinal activity, or when the muscular atrophy becomes prevalent[26,51]. The EMG pattern of muscles trunk activation was not associated to specific clinic and demographic features, and it was not a predictor of the clinical outcome. Although this data must be taken with caution because the present study was not powered to test for this hypothesis, it provides a relevant clinical insight. Indeed, t-DCS seems to be effective regardless of the underlying

EMG muscles activation, and therefore also in those PS phenotypes that are not amenable to a BTx-A treatment.

t-DCS is a non-invasive, well tolerated, easy repeatable and low-cost technique, and may represent a therapeutic alternative for those patients with contraindications to BTx-A (EMG pattern not suitable, or severe atrophy of the paraspinal muscles). Moreover, t-DCS does not interact with the underlying drug therapy, and therefore it is a suitable treatment for PD patients and, more in general, for the elderly population with multiple comorbidities. The tolerability and the ease of use of t-DCS open up new perspectives for the future, such as a combination approach with BTx-A injections, or a home-based neuromodulation approach, which already proved to be feasible in PD trough telerehabilitation[104].

Some limitations must be acknowledged for a comprehensive interpretation of our results. First, the small sample size of the present study does not allow to infer definitive conclusions. In addition, based on our inclusion/exclusion criteria, we enrolled a population without cognitive impairment and without the compelling need of frequent adjustments of the anti-parkinsonian treatment, which further reduced our cohort. Yet, the adaptability of t-DCS is one of its intrinsic limits, although we adopted a bi-hemispheric approach, but we cannot exclude that other stimulation paradigms might induce comparable or even better results.

CONCLUSIONS

Our findings support the use of a bi-hemispheric t-DCS approach as add-on to neurorehabilitation in the management of patients affected by PS and PD. t-DCS potentiates the positive effects of the rehabilitation treatment on the postural alterations in upright standing position, on the range of motion of the trunk during dynamic tasks as well as on functional independence, and lumbar pain severity. It is worth noting that the overall improvement in static posture of the trunk achieved in t-DCS group were more persistent and still retained at 6 months. t-DCS is a non-invasive, well tolerated, easy repeatable and low-cost technique, which may represent a therapeutic alternative for those patients with contraindications to botulinum toxin.

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