

RESEARCH ARTICLE

Transcranial stimulation in frontotemporal dementia: A randomized, double-blind, sham-controlled trial

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Classification of Evidence: This study provides Class II evidence that is effective and safe in FTD.

Abstract

Introduction: Frontotemporal dementia (FTD) is a progressive disease for which no curative treatment is currently available. We aimed to determine whether transcranial direct current stimulation (tDCS) can modulate intracortical connectivity and improve cognition in symptomatic FTD patients and presymptomatic FTD subjects.

Methods: We performed a double-blind, randomized, sham-controlled trial with anodal tDCS or sham stimulation over the left prefrontal cortex in 70 participants (15 presymptomatic and 55 symptomatic FTD).

Results: We observed a significant increase of intracortical connectivity (short interval intracortical inhibition and facilitation) and improvement in clinical scores and behavioral disturbances in both symptomatic FTD patients and presymptomatic carriers after real tDCS but not after sham stimulation.

Discussion: A 2-weeks' treatment with anodal left prefrontal tDCS improves symptoms and restores intracortical inhibitory and excitatory circuits in both symptomatic FTD patients and presymptomatic carriers. tDCS might represent a promising future therapeutic and rehabilitative approach in patients with FTD.

KEYWORDS

clinical trial, frontotemporal dementia, granulin, presymptomatic, short interval intracortical inhibition, transcranial direct current stimulation, transcranial magnetic stimulation

1 | INTRODUCTION

Frontotemporal dementia (FTD) is a progressive disease characterized by a broad series of symptoms, including personality and behavioral disturbances, language deficits, and impairment of executive functions.¹ Three phenotypic variants have been characterized based on the predominant clinical presentation and the pattern of frontotem-

poral atrophy, including the behavioral variant of FTD (bvFTD), the agrammatic variant of primary progressive aphasia (avPPA), and the semantic variant of PPA (svPPA).^{2,3} Three main genes account for 10% to 20% of FTD cases: *chromosome 9 open reading frame 72* (C9orf72), *granulin* (GRN), and *microtubule-associated protein tau* (MAPT).⁴

There is growing interest in finding innovative therapeutic approaches to improve clinical symptoms in patients with FTD.

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Recent studies using non-invasive brain stimulation, such as transcranial direct current stimulation (tDCS), have shown promising results on language performance in patients with PPA.⁵⁻⁸ It has been demonstrated that a single session of tDCS may determine a polarity-dependent modulation of cortical excitability, with effects that can last for up to a few hours after a single stimulation session, while multiple sessions are considered to induce cumulative and long-lasting after-effects, mediated by the modulation of cortical plasticity.⁹

However, clinical trials with tDCS in FTD currently lack reliable biomarkers to monitor intervention outcomes, particularly in the presymptomatic phases of disease. In this view, neurophysiological techniques, particularly transcranial magnetic stimulation (TMS), have become promising tools to assess specific cortical circuits in the central nervous system.¹⁰ Indeed, with the contribution of pharmacological studies, several TMS stimulation paradigms have been developed to assess, non-invasively, the function of GABAergic, and glutamatergic circuits,¹¹⁻¹³ which have been shown to be altered both in sporadic FTD patients¹⁴⁻¹⁷ and in presymptomatic carriers of a pathogenic mutation for FTD.¹⁸⁻²⁰ These parameters have been shown to correlate with both positive and negative neuropsychiatric symptoms²¹ and with disease progression.^{20,22}

These observations defined the objective of this work, aimed at assessing long-term effects of multiple sessions of anodal tDCS over the left prefrontal cortex (PFC) in symptomatic FTD patients and presymptomatic subjects carrying FTD pathogenetic mutations.

To this aim, we carried out a double-blind, randomized, sham-controlled clinical trial, and we assessed the effect of anodal tDCS on (a) intracortical connectivity measures as measured by TMS, and (b) clinical outcomes, selecting those tests tapping cognitive functions most affected since the earliest stages of disease.

2 | METHODS

2.1 | Standard protocol approvals, registrations, and patient consents

Full written informed consent was obtained from all participants according to the Declaration of Helsinki. The study protocol was approved by the local ethics committee (Brescia Hospital, #NP2441). This trial has been registered at ClinicalTrials.gov (NCT02999282).

2.2 | Participants

Seventy participants were recruited overall, including 15 presymptomatic carriers and 55 symptomatic patients. Presymptomatic carriers were defined as carriers of a pathogenic mutation in the *GRN* gene, who did not fulfill current criteria for bvFTD³ or PPA.²

Symptomatic patients were defined as patients fulfilling current criteria for bvFTD³ or PPA,² with a sporadic disease or carriers of a pathogenic mutation within *GRN*, *C9orf72*, or *MAPT* genes.

HIGHLIGHTS

- Frontotemporal dementia (FTD) is a progressive disease for which no curative treatment is currently available.
- We performed a double-blind, randomized, sham-controlled trial with transcranial direct current stimulation (tDCS).
- tDCS restored intracortical connectivity (intracortical inhibition and facilitation).
- tDCS improved clinical scores and behavioral disturbances.
- Results were observed in both symptomatic and presymptomatic FTD.

RESEARCH IN CONTEXT

1. **Systematic review:** The authors reviewed the literature using traditional (eg, PubMed) sources and meeting abstracts and presentations. Frontotemporal dementia (FTD) is a progressive disease for which no curative treatment is currently available and only few randomized controlled studies have been performed. Non-invasive brain stimulation techniques are emerging as novel treatments for several neurodegenerative disorders. These relevant citations are appropriately cited.
2. **Interpretation:** Our findings highlight an improvement in symptoms and intracortical inhibitory and excitatory circuits in both symptomatic FTD patients and presymptomatic carriers after 2-weeks' treatment with anodal left prefrontal transcranial direct current stimulation (tDCS) compared to placebo.
3. **Future directions:** The article proposes a framework for the generation of new hypotheses and the conduct of additional studies, emphasizing the role of non-invasive brain stimulation in modulating intracortical circuitry in both the presymptomatic and symptomatic phases of FTD.

Presymptomatic at risk subjects with an affected family member but without a pathogenic FTD mutation were also initially recruited but excluded from the present study. This was necessary so as to conceal which participants were actually carriers of a mutation, because presymptomatic at-risk subjects in most cases were unaware of their mutational status.

In sporadic patients, cerebrospinal fluid (CSF) analyses were performed to exclude focal Alzheimer's disease (AD) pathology, as previously reported.²³ Briefly, a CSF AD-like profile was defined as tau

≥ 400 ng/L and $A\beta_{42} \leq 600$ ng/L using an enzyme-linked immunosorbent assay (ELISA; INNOTEST, Innogenetics, Ghent, Belgium).²⁴

The following exclusion criteria were applied: (a) cerebrovascular disorders, previous stroke, hydrocephalus, and intra-cranial mass documented by magnetic resonance imaging (MRI); (b) history of traumatic brain injury or other neurological diseases; (c) serious medical illness other than FTD; (d) history of seizures; (e) pregnancy; (f) metal implants in the head (except dental fillings); (g) electronic implants (ie, pacemaker, implanted medical pump); (h) age <18 years.

Patients who were already on a pharmacologic regimen were allowed to receive treatment provided that the regimen remained unchanged, but initiation of drugs after the start of the observation period was not allowed.

In addition, 22 age- and sex-matched healthy controls (age 64.0 ± 11.5) were recruited as reference group for TMS parameters.

2.3 | Study design

Patients were recruited at the Centre for Neurodegenerative Disorders, University of Brescia, Italy from September 2017 to March 2019, with the follow-up ending in September 2019. Presymptomatic carriers and symptomatic patients were randomized into two groups: each group received anodal left PFC tDCS (real tDCS) or sham stimulation for 5 days/week for 2 weeks, in a 2:1 ratio, respectively.

Each participant underwent a clinical evaluation, according to a standardized clinical assessment (see clinical assessment below) and TMS analysis (see TMS analysis below) at baseline (pre-stimulation—the first day before anodal/sham stimulation, T0), immediately after 2 weeks of either real or sham tDCS (post-stimulation—the last day after anodal/sham stimulation, T1), at 1-month (T2—only TMS analysis), at 3-month (T3), and at 6-month follow-up (T4) from baseline (see Figure 1).

Five principal investigators were involved in experimentations: one performing neuropsychological evaluations (M.Cos.), two performing TMS at baseline and at follow-up (V.D., V.C.), and two performing tDCS (R.M., C.B.). The patients and the examiners performing clinical ratings, tDCS and TMS protocols were blinded to the type of stimulation. B.B. was responsible for random allocation sequences, enrollment of participants, allocation concealment, and assignment of participants to specific interventions.

2.4 | Clinical assessment

At each time point (T0, T1, T3, and T4), the following cognitive assessments were performed in both presymptomatic carriers and in symptomatic patients: Mini-Mental State Examination (MMSE), phonemic verbal fluency, trail making test (TMT-A and TMT-B), Stroop test, digit symbol substitution test, the modified Ekman emotion recognition test, and the Cambridge Behavior Inventory (CBI). To reduce variability in outcome parameters, cognitive testing was kept consistent between presymptomatic carriers and symptomatic patients. Excluding the very essential neuropsychological tests used (ie, MMSE), we implemented

tests which do not have a ceiling effect (ie, TMT-A and -B, Stroop test, and phonemic verbal fluency), or have been shown to be already altered in presymptomatic carriers (ie, digit symbol test and Ekman emotion recognition test), even in our cohort of presymptomatic carriers. These tests have been carefully selected from the GENFI study on presymptomatic carriers, in which these tests were the first to detect deviations from normality.²⁵

2.5 | Transcranial magnetic stimulation assessment

TMS was performed with a figure-of-eight coil (each loop diameter 70 mm) connected to a Magstim Bistim² system (Magstim Company, Oxford, UK), as previously reported.²⁶ The magnetic stimuli had a monophasic current waveform (rise time of 100 μ s, decaying back to zero over 800 μ s). Motor evoked potentials (MEPs) were recorded from the right first dorsal interosseous muscle (FDI) through surface Ag/AgCl electrodes placed in a belly-tendon montage and acquired using a Biopac MP-150 electromyograph (BIOPAC Systems Inc., Santa Barbara, CA, USA). The TMS coil was held tangentially over the scalp region corresponding to the primary hand motor area contralateral to the target muscle, with the coil handle pointed 45° posteriorly and laterally to the sagittal plane.

The motor hot spot was defined as the location where TMS consistently produced the largest MEP size in the target muscle. Resting motor threshold (rMT) was defined as the minimal stimulus intensity needed to produce MEPs with an amplitude of at least 50 μ V in 5 out of 10 consecutive trials during complete muscle relaxation, which was controlled by visually checking the absence of electromyography (EMG) activity at high-gain amplification.¹⁰

Short interval intracortical inhibition (SICI) and intracortical facilitation (ICF), which predominantly reflect GABA_Aergic and glutamatergic neurotransmission, respectively, were studied at rest via a paired-pulse paradigm, delivered in a conditioning-test design with the conditioning stimulus (CS) set at an intensity of 70% of the rMT, while the test stimulus (TS) was adjusted to evoke a MEP approximately 1 mV peak-to-peak in the relaxed FDI. Different interstimulus intervals (ISIs) between the CS and TS were used to investigate preferentially both SICI (1, 2, 3, 5 ms) and ICF (7, 10, 15 ms).^{12,27}

Long interval intracortical inhibition (LICI), which predominantly reflects GABA_Bergic transmission, was elicited by applying two suprathreshold stimuli at long ISIs (50, 100, 150 ms), with the CS set at 130% of the rMT preceding the TS, adjusted to evoke a MEP of approximately 1 mV peak-to-peak.²⁸

Ten stimuli were delivered for each ISI for all stimulation paradigms and 14 control MEPs in response to the TS alone were recorded, for each paradigm, in all participants in a pseudo-randomized sequence. The amplitude of the conditioning MEPs was expressed as a ratio of the mean unconditioned response. The inter-trial interval was set at 5 seconds ($\pm 10\%$).

Throughout the experiment, complete muscle relaxation was monitored by audio-visual feedback where appropriate. All patients were able to understand instructions and obtain full muscle relaxation.

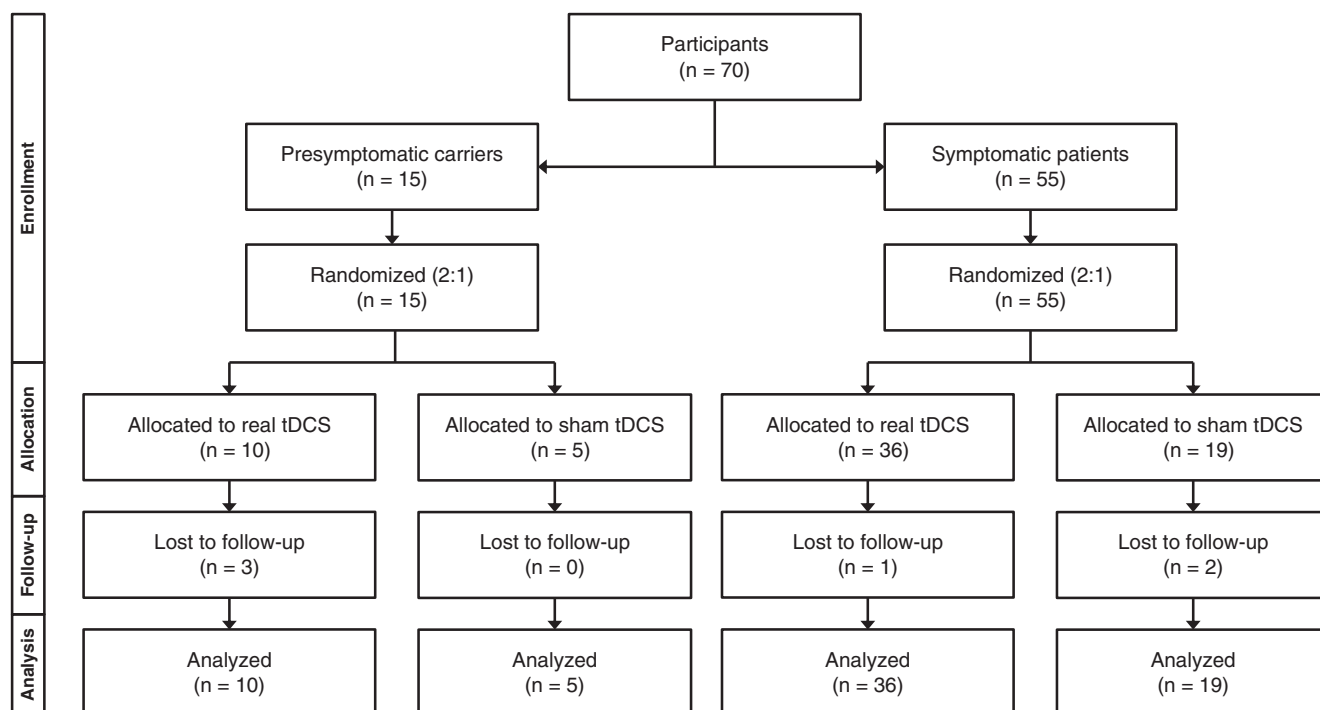


FIGURE 1 Study design. tDCS = transcranial direct current stimulation. TMS = transcranial magnetic stimulation

2.6 | Transcranial direct current stimulation

tDCS was delivered by a battery-driven constant current stimulator through a pair of saline-soaked (0.9% NaCl) surface sponge electrodes ($5 \times 7 \text{ cm}^2$). The active electrode (anode) was placed on the scalp over the left PFC (with the center over the F3 position according to the 10 to 20 international electroencephalogram coordinates) and the reference (cathode) over the right deltoid muscle, as reported in clinical applications.⁹ The electrodes were secured using elastic gauzes and electroconductive gel was applied to electrodes to reduce contact impedance ($<5 \text{ k}\Omega$ for all sessions).

During real stimulation, a constant current of 2 mA (current density: 0.06 mA/cm^2) was applied for 20 minutes. For the sham condition, the electrode placement was the same, but the electric current was ramped-down 5 seconds after the beginning of the stimulation to make this condition indistinguishable from the experimental stimulation. To detect differences in the perception of the stimulation, patients were asked whether they thought they received real or sham stimulation at the end of the 2-week session.

2.7 | Outcome measures

For efficacy analyses, the primary endpoint was defined as the change from baseline in neurophysiological measures (SICI, ICF, and LICI). These measures were chosen because they have been shown to be already altered also in presymptomatic carriers, long before the onset of clinical and behavioral disturbances.²⁰ Secondary endpoints were changes from baseline in neuropsychological tests.

2.8 | Statistical analyses

The number of included participants, stratified for disease state and corrected for possible dropouts, was assessed with a power analysis from preliminary results obtained on a small group of patients, considering 80% power and a 95% confidence interval (CI). Intention-to-treat analysis was performed. For patients with missing values at follow-up (see Figure 1), data were assigned using mixed effects models for repeated measures without any ad hoc imputation for both clinical and neurophysiological measures. To assess the effect of tDCS treatment on TMS parameters we used a three-way mixed analysis of variance (ANOVA) with TIME (T0, T1, T2, T3, and T4) and ISI (1, 2, 3, 5, 7, 10, and 15 ms) as within-subject factors, and TREATMENT (sham vs real stimulation) as between-subjects factor.

To assess the effect of tDCS treatment on clinical scores over time, we used a two-way mixed analysis of covariance (ANCOVA) with TIME (T0, T1, T3, and T4) as within-subject factors and TREATMENT (sham vs real stimulation) as between-subjects factor. Baseline values of each score, age, disease duration (only for affected symptomatic patients), and education were used as covariates, to reduce possible effects of baseline characteristics on clinical score changes over time.

Only when a significant main effect was reached, post hoc tests with Bonferroni correction for multiple comparisons were conducted to analyze group differences at respective time points (all *P* values are reported after Bonferroni adjustment for multiple comparisons). Mauchly's test was used to assess for assumption of sphericity, while Greenhouse–Geisser epsilon determination was used to correct in case of sphericity violation. Pearson's correlations were used to assess associations between the improvement in clinical scores and

neurophysiological parameters (P values are reported after Bonferroni adjustment for multiple comparisons).

Statistical analyses were performed using SPSS version 21 (SPSS, Inc., Chicago, IL, USA).

2.9 | Data availability

All data, including outcome measure results, study protocol, and statistical analysis plan, will be shared through ClinicalTrials.gov via public access (<https://clinicaltrials.gov/ct2/show/NCT02999282>).

3 | RESULTS

3.1 | Participants

Seventy subjects, of which 15 presymptomatic participants and 55 symptomatic FTD patients, were enrolled and randomized to receive real or sham stimulation in a 2:1 ratio. Six subjects dropped out from the study at T4: two symptomatic patients receiving sham stimulation (both cases for worsening of symptoms), one symptomatic patient receiving real stimulation (for geographical reasons and not for worsening of symptoms), three presymptomatic carriers receiving real stimulation (two for logistic reasons and one for desire of pregnancy and not for worsening of symptoms); no treatment-related adverse events were observed in both groups (see Figure 1).

Demographic characteristics of included patients are reported in Table 1. Among FTD patients, 25 bvFTD and 30 PPA were included. Moreover, 22 out of 55 FTD patients were pathogenetic mutations carriers ($n = 15$ GRN T272fs mutation, $n = 5$ C9orf72 expansion, and $n = 2$ MAPT P301L mutation).

Regarding the differences in the patients' perception of the stimulation, there was no statistically significant association between type of stimulation and perception, as assessed by Fisher's exact test ($P = 1.000$ for symptomatic patients; $P = 0.608$ for presymptomatic carriers), suggesting that real tDCS could not be distinguished from sham stimulation.

3.2 | Intracortical connectivity in FTD patients and in presymptomatic subjects

3.2.1 | Symptomatic patients

At the three-way mixed ANOVA performed on SICI-ICF we observed a statistically significant three-way TIME $\times$ ISI $\times$ TREATMENT interaction, $F(24,1248) = 6.19$, $P < 0.001$, partial $\eta^2 = 0.11$. There was a statistically significant simple two-way interaction between TIME and ISI for real stimulation, $F(24,816) = 13.70$, $P < 0.001$, partial $\eta^2 = 0.29$, but not for sham stimulation, $F(24,432) = 1.16$, $P = 0.274$, partial $\eta^2 = 0.06$. There were significant differences (increased SICI and ICF) at T1, T2, and T3, but not T4, compared to baseline (T0) for real stimulation but

not sham stimulation (for significant differences at individual ISIs; see Figure 2A and B).

No significant TIME $\times$ ISI $\times$ TREATMENT interaction was observed for LIC1 ($F(8,416) = 0.47$, $P = 0.880$, partial $\eta^2 = 0.01$).

Baseline and follow-up neurophysiological scores in real and sham tDCS group are reported in Table S1 in supporting information.

3.2.2 | Presymptomatic subjects

At the three-way mixed ANOVA performed on SICI-ICF we observed a statistically significant three-way TIME $\times$ ISI $\times$ TREATMENT interaction, $F(24,312) = 2.14$, $P = 0.002$, partial $\eta^2 = 0.14$. There was a statistically significant simple two-way interaction between TIME and ISI for real stimulation, $F(24,216) = 5.66$, $P < 0.001$, partial $\eta^2 = 0.39$, but not for sham stimulation, $F(24,96) = 0.41$, $P = 0.993$, partial $\eta^2 = 0.09$. There were significant differences (increased SICI and ICF) at T1, T2, and T3 but not T4 compared to baseline (T0) for real stimulation but not sham stimulation (for significant differences at individual ISIs see Figure 2C and D).

No significant TIME $\times$ ISI $\times$ TREATMENT interaction was observed for LIC1 ($F(8,104) = 0.61$, $p = 0.770$, partial $\eta^2 = 0.05$).

Baseline and follow-up neurophysiological scores in real and sham tDCS group are reported in Table S1.

3.3 | Clinical assessment in FTD patients

A two-way mixed ANCOVA was performed on cognitive assessments measures.

We observed a statistically significant TIME $\times$ TREATMENT interaction for MMSE $F(3,147) = 9.38$, $P < 0.001$, partial $\eta^2 = 0.16$ (Figure 3A); for phonemic verbal fluency, $F(3,147) = 8.52$, $P < 0.001$, partial $\eta^2 = 0.15$ (Figure 3B); for TMT-A, $F(3,147) = 8.99$, $P < 0.001$, partial $\eta^2 = 0.15$ (Figure 3C); for TMT-B, $F(3,147) = 5.47$, $P = 0.001$, partial $\eta^2 = 0.10$ (Figure 3D); for the Stroop test, $F(3,147) = 3.00$, $P = 0.033$, partial $\eta^2 = 0.06$ (Figure 3E); for the digit symbol substitution test, $F(3,147) = 7.76$, $P < 0.001$, partial $\eta^2 = 0.14$ (Figure 3F); for the modified Ekman emotion recognition test, $F(3,147) = 7.76$, $P < 0.001$, partial $\eta^2 = 0.14$ (Figure 3G); and for the CBI, $F(3,147) = 4.80$, $P = 0.003$, partial $\eta^2 = 0.09$ (Figure 3H). Significant differences after Bonferroni correction, at every time point and for each test, are reported in Figure 3A-H.

Baseline and follow-up neuropsychological scores in real and sham tDCS group are reported in Table S1.

3.4 | Clinical assessment in FTD patients according to phenotype and genetic trait

We conducted an exploratory subgroup analysis to evaluate the effect of tDCS in either bvFTD or PPA patients, reporting P values after Bonferroni correction for multiple comparisons. In bvFTD patients ($n = 25$) we observed a significant TIME $\times$ TREATMENT interaction for TMT-A, $F(3,57) = 5.77$, $P = 0.002$, partial $\eta^2 = 0.23$; for TMT-B,

TABLE 1 Demographic and clinical characteristics of included participants at baseline

Variable	FTD (all)	FTD Real tDCS	FTD Sham tDCS	P^a	Pre-FTD (all)	Pre-FTD Real tDCS	Pre-FTD Sham tDCS	P^b
N	55	36	19	-	15	10	5	-
Age, years	62.0 ± 7.2	62.4 ± 7.0	61.4 ± 7.4	0.66	52.5 ± 9.6	50.8 ± 8.8	55.1 ± 11.4	0.36
Sex, female %	54.5	52.8	57.9	0.78	60.0	70.0	40.0	0.26
Age at onset, years	59.1 ± 7.4	59.4 ± 7.2	58.5 ± 8.1	0.68	-	-	-	-
Education, years	12.1 ± 4.0	12.2 ± 4.4	11.0 ± 3.1	0.75	11.3 ± 4.0	11.0 ± 3.5	12.0 ± 5.4	0.67
Phenotype, bvFTD %	45.5	47.2	42.1	0.78	-	-	-	-
Pathogenetic mutations, %	40.0	36.1	47.4	0.55	100	100	100	-
<i>Cognitive assessment</i>								
MMSE	19.7 ± 9.4	20.2 ± 9.2	18.8 ± 9.8	0.60	28.9 ± 0.9	29.0 ± 0.8	28.8 ± 1.5	0.72
Phonemic verbal fluency	13.9 ± 9.1	13.4 ± 9.4	14.9 ± 8.6	0.56	-	-	-	-
Trail Making test, A (sec)	87.7 ± 52.1	92.5 ± 52.7	78.7 ± 51.2	0.35	29.5 ± 8.7	28.0 ± 4.8	32.6 ± 14.0	0.35
Trail Making test, B (sec)	231.9 ± 89.6	232.5 ± 93.0	230.7 ± 85.0	0.94	90.8 ± 65.0	83.1 ± 33.5	106.2 ± 108.8	0.53
Stroop test	86.8 ± 42.7	94.7 ± 45.7	71.9 ± 32.4	0.06	29.4 ± 9.8	31.0 ± 8.5	26.2 ± 12.5	0.39
Digit symbol	21.2 ± 16.0	20.4 ± 16.8	22.7 ± 14.7	0.62	48.9 ± 14.4	48.0 ± 14.3	44.6 ± 15.8	0.69
Ekman emotion recognition	14.4 ± 9.3	13.8 ± 8.8	15.6 ± 10.3	0.50	26.4 ± 3.4	25.6 ± 2.4	28.0 ± 4.8	0.22
CBI	60.0 ± 33.2	61.9 ± 35.1	56.2 ± 29.8	0.55	-	-	-	-
<i>TMS</i>								
Mean SICI (1, 2, 3 ms)	0.67 ± 0.28	0.67 ± 0.29	0.67 ± 0.27	0.97	0.36 ± 0.20	0.38 ± 0.24	0.34 ± 0.09	0.72
Mean ICF (7, 10, 15 ms)	0.99 ± 0.30	1.01 ± 0.26	0.98 ± 0.37	0.78	0.94 ± 0.12	0.95 ± 0.07	0.90 ± 0.20	0.49
Mean LICI (50, 100, 150 ms)	0.70 ± 0.34	0.62 ± 0.34	0.79 ± 0.34	0.35	0.61 ± 0.46	0.63 ± 0.50	0.59 ± 0.42	0.43

Abbreviations: bvFTD, behavioral variant FTD; CBI, Cambridge Behavior Inventory; FTD, frontotemporal dementia; ICF, intracortical facilitation; LICI, long interval intracortical inhibition; MMSE, Mini-Mental State Examination; pre-FTD, preclinical FTD; SICI, short interval intracortical inhibition; tDCS, transcranial direct current stimulation; TMS, Transcranial Magnetic Stimulation.

^aFTD real tDCS versus FTD sham tDCS.

^bpre-FTD real tDCS versus pre-FTD sham tDCS; P values after Student t test or χ -square's test, as appropriate; results are expressed as mean ± standard deviation unless otherwise specified.

$F(3,57) = 3.96$, $P = 0.012$, partial $\eta^2 = 0.17$; for the modified Ekman emotion recognition test, $F(3,57) = 5.66$, $P = 0.002$, partial $\eta^2 = 0.23$; but not for MMSE, phonemic verbal fluency, Stroop test, digit symbol substitution test, and CBI.

In PPA patients ($n = 30$), we observed a significant TIME × TREATMENT interaction for MMSE, $F(3,72) = 10.64$, $P < 0.001$, partial $\eta^2 = 0.31$; for phonemic verbal fluency, $F(3,72) = 6.19$, $P = 0.001$, partial $\eta^2 = 0.21$; for TMT-A, $F(3,72) = 7.27$, $P < 0.001$, partial $\eta^2 = 0.23$; for TMT-B, $F(3,72) = 3.53$, $P = 0.019$, partial $\eta^2 = 0.13$; for the digit symbol substitution test, $F(3,72) = 5.98$, $P = 0.001$, partial $\eta^2 = 0.20$; for the modified Ekman emotion recognition test, $F(3,72) = 5.74$, $P = 0.001$, partial $\eta^2 = 0.19$; for the CBI, $F(3,72) = 4.37$, $P = 0.007$, partial $\eta^2 = 0.15$; but not for the Stroop test.

When we considered the effect of genetic trait, we did not observe a significant TIME × TREATMENT × TRAIT interaction at the three-way mixed ANCOVA for all neuropsychological tests (all $P > 0.05$); however, we observed a statistically significant two-way interaction between TIME and TREATMENT (all $P < 0.025$) for all tests. All other two-way interactions were not statistically significant ($P > 0.05$), suggesting there was no significant difference in neu-

ropsychological scores between patients with and without a genetic mutation.

3.5 | Clinical assessment in presymptomatic FTD subjects

We observed a statistically significant TIME × TREATMENT interaction for the Stroop test, $F(3,30) = 4.23$, $P = 0.013$, partial $\eta^2 = 0.30$ (Figure 4A); and for the modified Ekman emotion recognition test, $F(3,30) = 5.92$, $P = 0.027$, partial $\eta^2 = 0.29$ (Figure 4B). Significant differences at every time point for each test are reported in Figure 4A-B.

No significant interactions were observed for MMSE, $F(3,30) = 2.38$, $p = 0.079$, partial $\eta^2 = 0.20$; for TMT-A, $F(3,30) = 1.51$, $P = 0.231$, partial $\eta^2 = 0.13$; for TMT-B, $F(3,30) = 2.77$, $P = 0.058$, partial $\eta^2 = 0.22$; and for the digit symbol substitution test, $F(3,30) = 0.47$, $P = 0.702$, partial $\eta^2 = 0.05$.

Baseline and follow-up neuropsychological scores in real and sham tDCS groups are reported in Table S1.

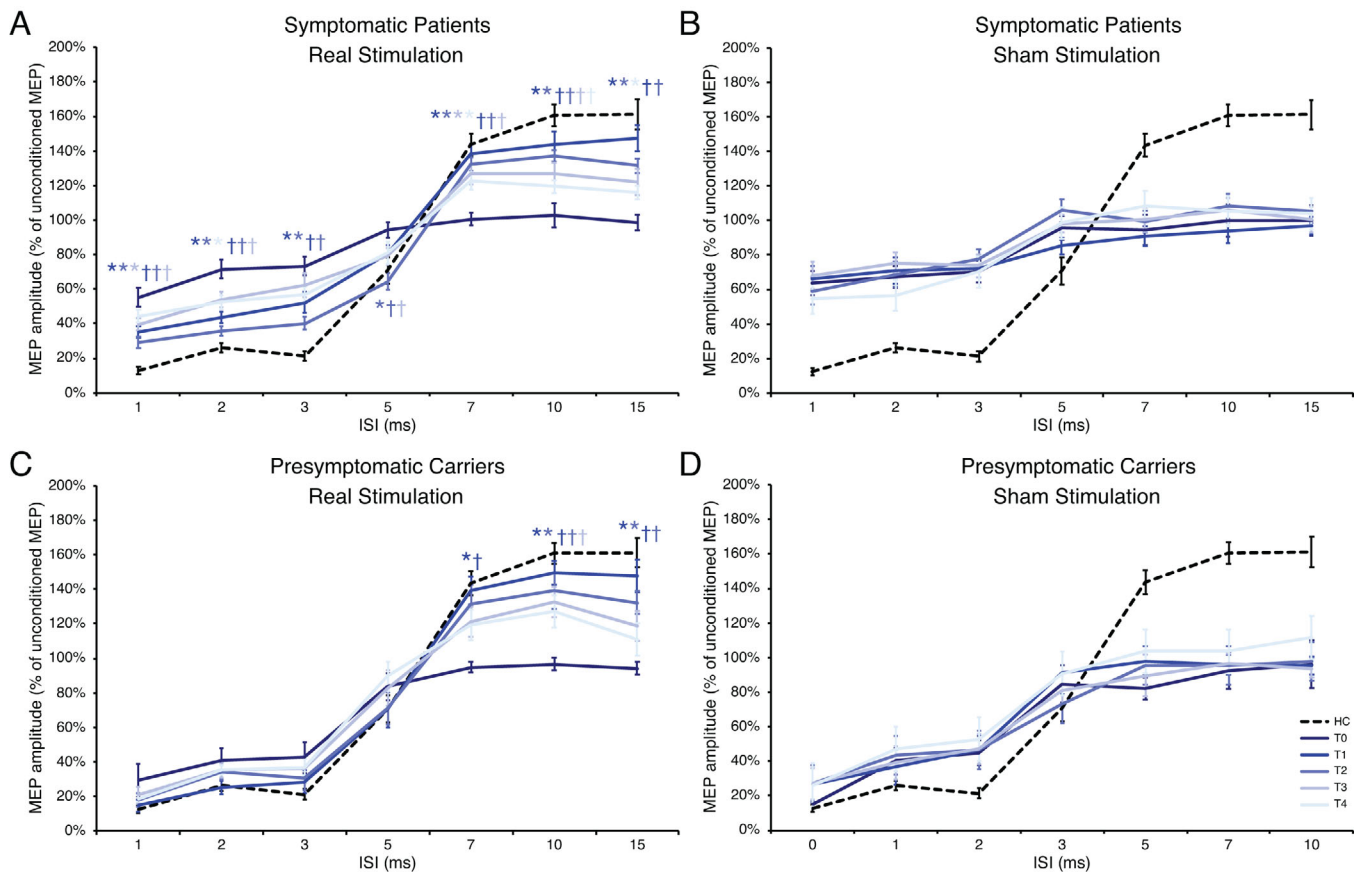


FIGURE 2 Neurophysiological measures of included subjects at different time points. ICF = intracortical facilitation; SICI = short interval intracortical inhibition; pre- and post-sham or real transcranial direct current stimulation (tDCS) at different time points (T0: baseline; T1: after 2-weeks' treatment; T2: at 1-month follow-up; T3 at 3-month follow-up; T4 at 6-month follow-up); error bars represent standard errors. A, real tDCS in frontotemporal dementia (FTD) patients; B, sham tDCS in FTD patients; C, real tDCS in presymptomatic FTD patients; D, sham tDCS in presymptomatic FTD patients. Black dotted line represents the mean value of average short interval intracortical inhibition and average intracortical facilitation of 22 age- and sex-matched healthy controls. * Significant difference from baseline (T0); † significant difference compared to sham stimulation

3.6 | Correlation between clinical and neurophysiological measures

A Pearson's product-moment correlation was run to assess the relationship between the percentage of average change in clinical scores after real stimulation, and neurophysiological measures. In symptomatic patients, there was a positive moderate correlation between the improvement at the TMT-A ($r = 0.36$, $P = 0.008$), TMT-B ($r = 0.37$, $P = 0.007$), Stroop test ($r = 0.433$, $P = 0.001$), and the increase of average ICF. In presymptomatic carriers, we observed a positive strong correlation between the improvement in the modified Ekman emotion recognition test and the increase in average ICF ($r = 0.58$, $P = 0.022$).

4 | DISCUSSION

In the present double-blind, randomized, sham-controlled trial, we observed a significant improvement or stabilization in neurophysiolog-

ical and clinical scores, at short and long term after a 2-weeks' treatment with left PFC anodal tDCS in FTD patients and in presymptomatic carriers of pathogenic FTD mutations. The current study confirms and extends previous work on the positive effects of tDCS on cognition in FTD.^{5-8,29-32} Beyond providing proof-of-concept for the efficacy of tDCS in a large cohort of subjects and with a robust study design, we observed that anodal tDCS is effective in bvFTD and in PPA phenotypes, both in patients with a sporadic or genetic disease. Furthermore, we argued for possible long-lasting effects of tDCS and, more interestingly, we demonstrated results in the presymptomatic stages, where anodal tDCS led to an improvement of cognitive functions, while in symptomatic phases tDCS reduced disease progression over time.

Last, the results herein presented were corroborated by intracortical connectivity parameters, as measured by TMS. Both in symptomatic and presymptomatic FTD, the effect of tDCS was accomplished by the improvement of glutamatergic (ie, ICF) and GABAergic (ie, SICI) neurotransmission, which paralleled cognitive trend. Indeed, it is now widely accepted that FTD is characterized by neurochemical changes

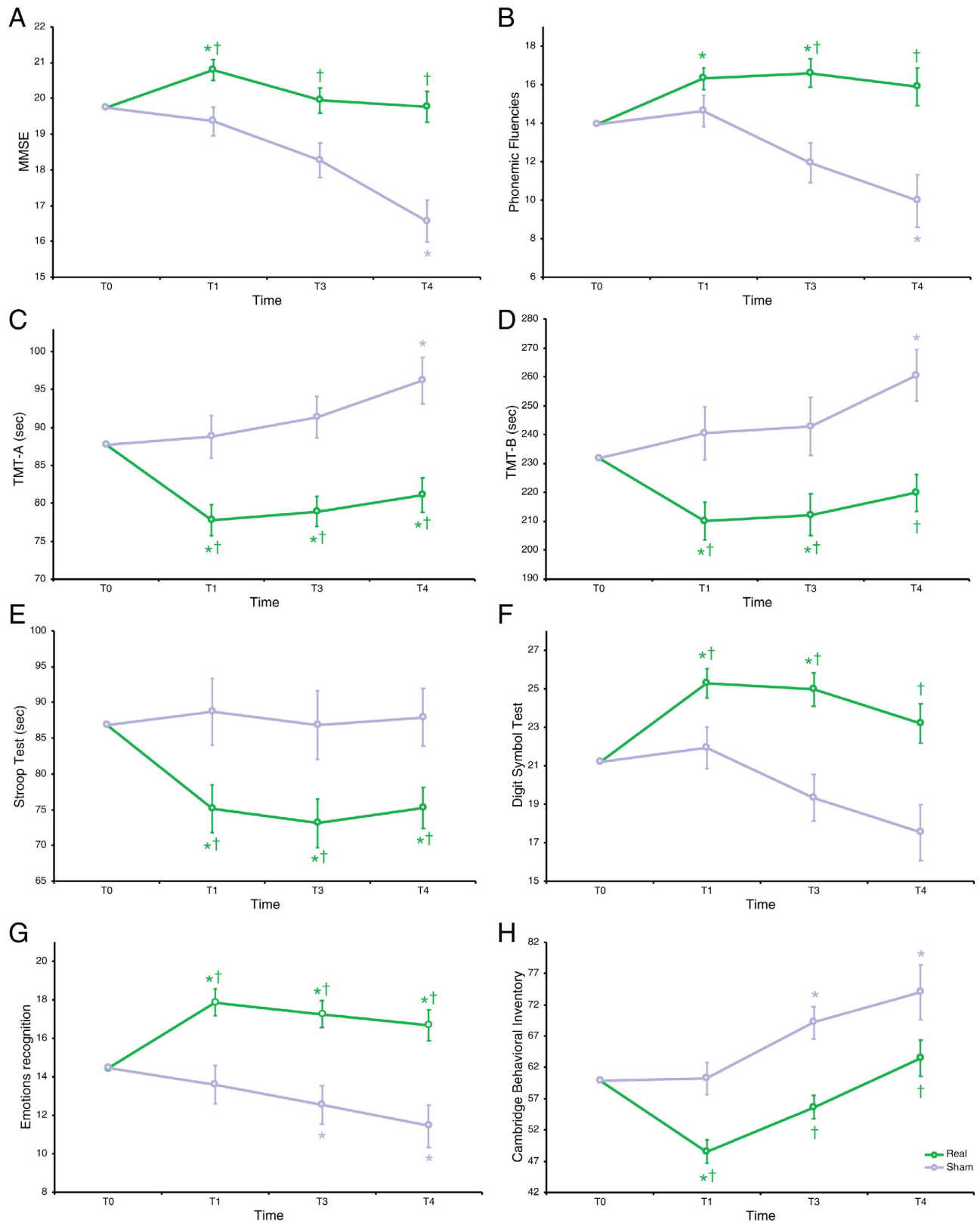


FIGURE 3 Significant differences of cognitive assessment tests in frontotemporal dementia (FTD) patients at different time points. Cognitive assessment pre- and post-sham and real transcranial direct current stimulation (tDCS) at different time points (T0: baseline; T1: after 2-weeks' treatment; T3 at 3-month follow-up; T4 at 6-month follow-up); Error bars represent standard errors. A, Mini Mental State Examination; B, Phonemic verbal fluency; C, Trail Making Test part A; D, Trail Making Test part B; E, Stroop test; F, Digit symbol substitution test; G, modified Ekman emotion recognition test; H, Cambridge Behavioral Inventory. *Significant difference from baseline (T0); †significant difference compared to sham stimulation

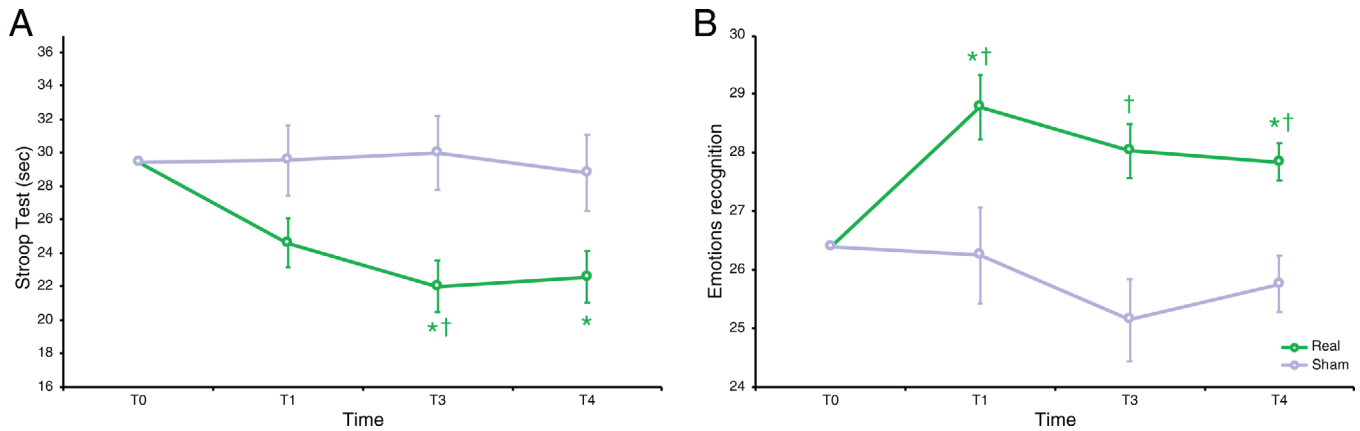


FIGURE 4 Significant differences of cognitive assessment tests in presymptomatic frontotemporal dementia (FTD) subjects at different time points. Cognitive assessment pre- and post-sham and real transcranial direct current stimulation (tDCS) at different time points (T0: baseline; T1: after 2-weeks' treatment; T3 at 3-month follow-up; T4 at 6-month follow-up); Error bars represent standard errors. A, Stroop Test; B, modified Ekman emotion recognition test. *Significant difference from baseline (T0); †significant difference compared to sham stimulation

that may contribute to the symptomatology of FTD, over and above neuronal loss and atrophy, with particular involvement of GABAergic and glutamatergic neurotransmission.^{33,34} In the same view, it has been clearly demonstrated that SIC1 and ICF intracortical connectivity measures, which are *in vivo* indirect markers of glutamatergic and GABAergic neurotransmission, respectively, are impaired since the earliest disease stages.¹⁴⁻¹⁷

Indeed, the mechanism by which tDCS leads to synaptic plasticity and, in turn, to the improvement of neurotransmitters and possible long-lasting effects, is still unanswered. However, mechanisms of long-term potentiation may explain the persistent effects on cortical activity, and in animal models these effects have been demonstrated to be mediated by glutamatergic receptors activation and brain derived neurotrophic factor (BDNF) secretion.^{35,36} Moreover, a possible role of tDCS-induced astrocytic modulation of N-methyl D-aspartate receptor (NMDAR)-dependent synaptic plasticity has been proposed.³⁷

The modulation of intracortical connectivity by left PFC anodal stimulation, possibly associated with an increase in cortical plasticity, may explain its effect on cognitive performance. Several studies have demonstrated a promising effect of anodal tDCS over the PFC on cognitive abilities in healthy aging and in neurodegenerative disorders,^{9,29-32} while very few studies have evaluated the effects of tDCS in patients with FTD, with almost all focusing on the treatment of language deficits in patients with PPA.⁵⁻⁸ In the present study, in both presymptomatic and symptomatic FTD, we found that anodal tDCS significantly improved executive functions and emotion recognition performance. More interestingly, in patients with FTD, the improvement in neuropsychological scores was further corroborated by caregivers, which reported a significant improvement of neuropsychiatric symptoms on the CBI.

We acknowledge that the present study entails some limitations. First, study design implied 2-weeks' treatment over the left PFC, selected according to current literature data and consensus; tDCS parameters, such as treatment duration, current amplitude, and site of stimulation, should be investigated further. Second, predictors of clinical

response, such as clinical profile or biological markers (ie, serum neurofilaments light chain or BDNF dosages), need to be assessed. Moreover, the sample size of the presymptomatic group was relatively small, which was, however, supported by a power analysis previously performed on a smaller group; nevertheless, results should be interpreted with caution at this stage. Finally, the evaluation of the add-on effect of tDCS to other pharmacological interventions or language training might be of interest to obtain synergic effects.

However, taken together, the results observed in clinical assessments and intracortical connectivity measures imply that tDCS will be undoubtedly of interest in routine clinical practice in the future, largely due to the excellent benefit-risk ratio.⁹ tDCS is a small and painless device that it is easy to use in clinical settings without requiring sophisticated neuronavigational techniques and knowledge, and at-home remotely supervised deployment has already been demonstrated as feasible in several studies.³⁸

In conclusion, in the light of limited pharmacologic and non-pharmacologic treatment options for patients with FTD, based on the results of this study, a 2-weeks' treatment with anodal PFC tDCS could be considered a potentially promising therapeutic approach, even in the presymptomatic stages of disease. Future studies evaluating whether the repetition of multiple tDCS sessions could increase both the duration and extent of clinical improvement are warranted.

CONFLICTS OF INTEREST

A. Benussi, V. Dell'Era, M. Cosseddu, V. Cantoni, M.S. Cotelli, M. Cotelli, R. Manenti, L. Benussi, C. Brattini, A. Alberici, B. Borroni, report no disclosures relevant to the manuscript.

AUTHOR CONTRIBUTIONS

Alberto Benussi, and Barbara Borroni contributed to the conception and design of the study. Alberto Benussi, Valentina Dell'Era, Valentina

Cantoni, Maura Cosseddu, Maria Sofia Cotelli, Maria Cotelli, Rosa Manenti, Luisa Benussi, Chiara Brattini, Antonella Alberici, and Barbara Borroni contributed to acquisition and analysis of data. Alberto Benussi, Valentina Dell'Era, and Barbara Borroni contributed to statistical analysis, drafting the text, and preparing the figures.

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REFERENCES

1. Lund The, Groups Manchester. Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. *J Neurol Neurosurg Psychiatry*. 1994;57:416-418.
2. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology*. 2011;76:1006-1014.
3. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134:2456-2477.
4. Borroni B, Padovani A. Dementia: a new algorithm for molecular diagnostics in FTL. *Nat Rev Neurol*. 2013;9:241-242.
5. Cotelli M, Manenti R, Petesi M, et al. Treatment of primary progressive aphasia by transcranial direct current stimulation combined with language training. *J Alzheimers Dis*. 2014;39:799-808.
6. Cotelli M, Manenti R, Paternicò D, et al. Grey matter density predicts the improvement of naming abilities after tDCS intervention in agrammatic variant of primary progressive aphasia. *Brain Topogr*. 2016;29:738-751.
7. Teichmann M, Lesoil C, Godard J, et al. Direct current stimulation over the anterior temporal areas boosts semantic processing in primary progressive aphasia. *Ann Neurol*. 2016;80:693-707.
8. Tsapkin K, Webster KT, Ficek BN, et al. Electrical brain stimulation in different variants of primary progressive aphasia: a randomized clinical trial. *Alzheimer's Dement Transl Res Clin Interv*. 2018;4:461-472.
9. Lefaucheur JP, Antal A, Ayache SS, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol*. 2017;128:56-92.
10. Rossini PM, Burke D, Chen R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol*. 2015;126:1071-1107.
11. Kujirai T, Caramia MD, Rothwell JC, et al. Corticocortical inhibition in human motor cortex. *J Physiol*. 1993;471:501-519.
12. Ziemann U, Rothwell JC, Ridding MC. Interaction between intracortical inhibition and facilitation in human motor cortex. *J Physiol*. 1996;496:873-881.
13. Ziemann U, Reis J, Schwenkreis P, et al. TMS and drugs revisited 2014. *Clin Neurophysiol*. 2015;126:1847-1868.
14. Benussi A, Di Lorenzo F, Dell'Era V, et al. Transcranial magnetic stimulation distinguishes Alzheimer disease from frontotemporal dementia. *Neurology*. 2017;89:665-672.
15. Padovani A, Benussi A, Di Lorenzo F, et al. Sensitivity and specificity of transcranial magnetic stimulation for differential diagnosis of Alzheimer's disease and frontotemporal dementia. *Alzheimer's Dement*. 2017;13:P695-P696.
16. Benussi A, Alberici A, Ferrari C, et al. The impact of transcranial magnetic stimulation on diagnostic confidence in patients with Alzheimer disease. *Alzheimers Res Ther*. 2018;10:94.
17. Benussi A, Grassi M, Palluzzi F, et al. Classification accuracy of transcranial magnetic stimulation for the diagnosis of neurodegenerative dementias. *Ann Neurol*. 2020;87(3):394-404.
18. Benussi A, Cosseddu M, Filaretto I, et al. Impaired long-term potentiation-like cortical plasticity in presymptomatic genetic frontotemporal dementia. *Ann Neurol*. 2016;80:472-476.
19. Gazzina S, Benussi A, Premi E, et al. Neuroanatomical correlates of transcranial magnetic stimulation in presymptomatic Granulin Mutation Carriers. *Brain Topogr*. 2018;31:488-497.
20. Benussi A, Gazzina S, Premi E, et al. Clinical and biomarker changes in presymptomatic genetic frontotemporal dementia. *Neurobiol Aging*. 2019;76:133-140.
21. Benussi A, Dell'Era V, Cantoni V, et al. Neurophysiological correlates of positive and negative symptoms in frontotemporal dementia. *J Alzheimers Dis*. 2020;73(3):1133-1142.
22. Benussi A, Dell'Era V, Cantoni V, et al. TMS for staging and predicting functional decline in frontotemporal dementia. *Brain Stimul*. 2020;13(2):386-392.
23. Borroni B, Benussi A, Cosseddu M, Archetti S, Padovani A. Cerebrospinal fluid tau levels predict prognosis in non-inherited frontotemporal dementia. *Neurodegener Dis*. 2014;13:224-229.
24. Borroni B, Benussi A, Archetti S, et al. Csf p-tau181/tau ratio as biomarker for TDP pathology in frontotemporal dementia. *Amyotroph Lateral Scler Front Degener*. 2015;16:86-91.
25. Rohrer JD, Nicholas JM, Cash DM, et al. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis. *Lancet Neurol*. 2015;14:253-262.
26. Benussi A, Dell'Era V, Cantoni V, et al. Discrimination of atypical parkinsonisms with transcranial magnetic stimulation. *Brain Stimul*. 2018;11:366-373.
27. Kujirai T, Sato M, Rothwell JC, Cohen LG. The effect of transcranial magnetic stimulation on median nerve somatosensory evoked potentials. *Electroencephalogr Clin Neurophysiol*. 1993;89:227-234.
28. Valls-Solé J, Pascual-Leone A, Wassermann EM, Hallett M. Human motor evoked responses to paired transcranial magnetic stimuli. *Electroencephalogr Clin Neurophysiol*. 1992;85:355-364.
29. Hsu WY, Zanto TP, Anguera JA, Lin YY, Gazzaley A. Delayed enhancement of multitasking performance: effects of anodal transcranial direct current stimulation on the prefrontal cortex. *Cortex*. 2015;69:175-185.
30. Medvedeva A, Materassi M, Neacsu V, et al. Effects of anodal transcranial direct current stimulation over the ventrolateral prefrontal cortex on episodic memory formation and retrieval. *Cereb Cortex*. 2019;29:657-665.
31. Meinzer M, Lindenberg R, Phan MT, Ulm L, Volk C, Flöel A. Transcranial direct current stimulation in mild cognitive impairment: behavioral effects and neural mechanisms. *Alzheimer's Dement*. 2015;11:1032-1040.
32. Dayan E, Censor N, Buch ER, Sandrini M, Cohen LG. Noninvasive brain stimulation: from physiology to network dynamics and back. *Nat Neurosci*. 2013;16:838-844.
33. Benussi A, Alberici A, Buratti E, et al. Toward a glutamate hypothesis of frontotemporal dementia. *Front Neurosci*. 2019;13:304.
34. Murley AG, Rowe JB. Neurotransmitter deficits from fronto temporal lobar degeneration. *Brain*. 2018;141:1263-1285.
35. Fritsch B, Reis J, Martinowich K, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. *Neuron*. 2010;66:198-204.
36. Podda MV, Cocco S, Mastrodonato A, et al. Anodal transcranial direct current stimulation boosts synaptic plasticity and memory in mice via epigenetic regulation of Bdnf expression. *Sci Rep*. 2016;6:22180.
37. Monai H, Ohkura M, Tanaka M, et al. Calcium imaging reveals glial involvement in transcranial direct current stimulation-induced plasticity in mouse brain. *Nat Commun*. 2016;7:1-10.

38. Sivaramakrishnan A, Datta A, Bikson M, Madhavan S. Remotely supervised transcranial direct current stimulation: a feasibility study for amyotrophic lateral sclerosis. *NeuroRehabilitation*. 2019;45:369-378.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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