Motor cortex tRNS improves pain, affective and cognitive impairment in patients with fibromyalgia: preliminary results of a randomised sham-controlled trial

M. Curatolo[1], G. La Bianca[1], G. Cosentino[1], R. Baschi[1], G. Salemi[1], R. Talotta[2], M. Romano[3], G. Triolo[4], M. De Tommaso[5], B. Fierro[1], F. Brighina[1]

[1]Department of Experimental Biomedicine and Clinical Neuroscience (BioNec), Neurology Section, University of Palermo, Italy;
[2]Rheumatology Unit, ASST-Fatebenefratelli-L. Sacco University Hospital, Milan, Italy.
[3]Operative Unit of Neurology, Ospedali Riuniti Villa Sofia, Cervello, Palermo, Italy;
[4]Biomedical Department of Internal and Specialist Medicine (DIBIMIS), Rheumatology Section, University of Palermo, Italy;
[5]Department of Basic Medical Science, Neuroscience and the Sensory System (SMBNOS), Neurophysiopathology of Pain Unit, Aldo Moro University of Bari, Italy.

Massimiliano Curatolo, PhD
Giuseppe La Bianca, MD
Giuseppe Cosentino, MD, PhD
Roberta Baschi, MD
Giuseppe Salemi, MD, PhD, Assoc. Prof.
Rossella Talotta, MD, PhD
Marcello Romano, MD
Giovanni Triolo, MD, Prof.
Marina De Tommaso, MD, Assoc. Prof.
Brigida Fierro, MD, Prof.
Filippo Brighina, MD, Assoc. Prof.

Please address correspondence to:
Dr Filippo Brighina,
Dept. of Experimental Biomedicine and Clinical Neuroscience (BioNeC),
Via del Vespro 143,
University of Palermo,
90127 Palermo, Italy.
E-mail: filippo.brighina@unipa.it

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ABSTRACT

Objective. *Fibromyalgia (FM) is a clinical syndrome characterised by widespread musculoskeletal pain, chronic fatigue, cognitive deficits, and sleep and mood disorders. The effectiveness of most pharmacological treatments is limited, and there is a need for new, effective and well-tolerated therapies. It has recently been shown that transcranial direct-current stimulation (tDCS) of the motor cortex reduces pain, and that tDCS of the dorso-lateral prefrontal cortex (DLPFC) improves anxiety, depression and cognitive impairment in FM patients. The new technique of transcranial random noise stimulation (tRNS) using randomly changing alternating currents has very recently been shown to improve working memory and pain in limited series of patients with FM or neuropathic pain. The aim of this study was to investigate the clinical effects of primary motor cortex (M1) tRNS in FM patients.*

Methods. *Twenty female FM patients aged 26-67 years were randomised to undergo active (real) or placebo (sham) tRNS sessions on five days a week (Monday-Friday) for two weeks. Each patient was evaluated before and after treatment using a visual analogue scale (VAS), the Fibromyalgia Impact Questionnaire (FIQ), the Hospital Anxiety and Depression Scale (HADS), the Trail Making Test (TMT), the Rey Auditory Verbal Learning Test (RAVLT), the Forward and Backward Digit Span test, and the FAS verbal fluency test.*

Results. *In comparison with sham treatment, active tRNS of M1 induced a general improvement in the clinical picture of FM, with a significant reduction in pain, depression, anxiety and FIQ scores and a significant improvement in TMT (A), RAVLT and FAS scores.*

Conclusion. *These findings suggest that tRNS of M1 can be very effective in relieving FM symptoms. Unlike motor cortex tDCS, it seems to counteract both pain and cognitive disturbances, possibly because the invoked mechanism of stochastic resonance synchronises neural firing and thus leads to more widespread and lasting effects.*

Introduction

Fibromyalgia (FM) is a multifaceted clinical syndrome in which a painful disorder characterised by widespread musculoskeletal involvement is associated with a constellation of symptoms ranging from chronic fatigue to impaired cognitive and affective functions and even abnormal skin reactivity to various substances (1-6).

The disease affects 2–8% of people aged 20–40 years, mainly women (7-8), and the pain and associated symptoms often make it severely disabling, ensure that it has a major impact on the patients' everyday activities and quality of life (9-10), and lead to substantial direct and indirect socio-economic costs (11). In addition to pain, the particularly frequent and disabling symptoms of fatigue and cognitive impairment frequently affect attention, memory and executive functions, giving rise to a quite specific picture that is globally defined as "fibrofog" (12).

Various pharmacological and non-pharmacological approaches can be used to treat FM, but the efficacy of all of the treatments currently available is limited or short-lasting, and there is a real need for new, effective and well-tolerated alternatives (3-13). A neurophysiological approach based on non-invasive brain stimulation (NIBS) has recently been found to be potentially useful for treating neuropsychiatric

diseases and pain conditions. Two NIBS techniques have been developed: transcranial magnetic stimulation (TMS) based on magnetic fields, and transcranial electrical stimulation (tES) based on low-amperage electrical currents. The latter has aroused particular interest because it is inexpensive, easy to use, and only requires small stimulators that are suitable for self-use and open up the prospect of home-based treatment. The most widely studied tES application is transcranial direct-current stimulation (tDCS), which uses the delivery of direct current to affect the polarisation of neural cells: anodal currents favour depolarisation, thus increasing excitability and the propensity to neural firing, whereas cathodal stimulation does the reverse. It seems to have therapeutic potential in the case of FM as tDCS studies targeting the motor cortex have shown improvements in pain, and stimulation of dorso-lateral prefrontal cortex (DLPFC) improves anxiety, depression and cognitive impairments (14).

A further application of tES is transcranial random noise stimulation (tRNS), which is based on randomly changing alternating currents and has proved to be more effective in facilitating the motor cortex of healthy controls than anodal tDCS (15-16). Motor cortex tRNS has also improved neuropathic pain in a few case series (17), and a more recent study has found that it significantly improved pain and cognitive dysfunction in patients with multiple sclerosis (18).

The aim of this study was to investigate the ability of repeated tRNS sessions targeting the motor cortex to improve pain and its associated symptoms in a group of patients with FM.

Methods

Participants

The study recruited 20 female patients (mean age 42.8±9.87 years) with diagnosis of FM based on the 1990 American College of Rheumatology (ACR) criteria and at least one cognitive deficit. The Mini-Mental State Examination (MMSE) was used to exclude subjects with a substantial cognitive impairment (a score of >25), and patients with cognitive dysfunctions secondary to neurological or psychiatric diseases, a history of drug abuse or head trauma were also excluded.

The patients were recruited at Rheumatology Unit of "Paolo Giaccone" Polyclinic University Hospital, Palermo, and were treated at the Neurophysiopathology Unit of the same hospital. All of the participants gave their written, informed consent, and the study was approved by the local Ethics Committee.

Experimental design

The patients were randomised to undergo active (real) or placebo (sham) tRNS sessions on five days a week (Monday-Friday) for two weeks (Fig. 1). No concomitant pharmacological treatment was started, discontinued or modified during the study.

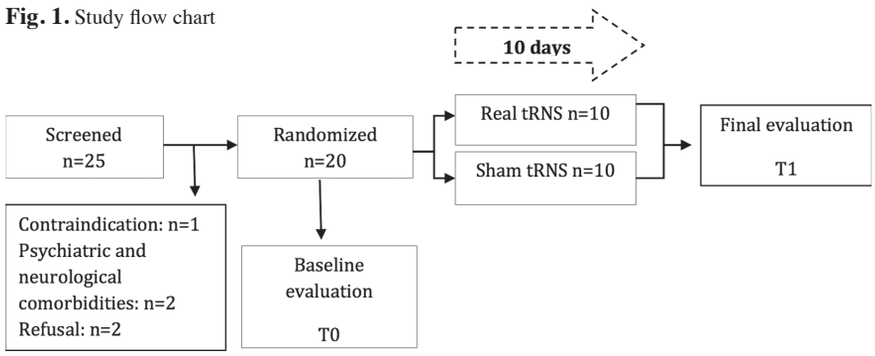
tRNS stimulation

A battery-powered BrainStim EMS stimulator was used to generate an electric current that was transmitted through wires to electrodes placed on the scalp. The 4.5 x 4.5 cm electrodes were covered by 7 x 6.5 cm sponges soaked in saline solution in order to minimise impedance. Using the 10–20 system, the electrodes were placed over C3 and on the right supra-orbital region, and secured by elastic laces. In the case of active tRNS, a constant current of 1.5 mA randomly oscillating in the frequency range of 101-640 Hz was applied for 10 minutes, with the offset set to 0 mA; in the case of the sham tRNS, the stimulation was turned on for only 30 seconds.

Measures

Each patient was evaluated, before and after treatment using a visual analogue scale (VAS), the Fibromyalgia Impact Questionnaire (FIQ), the Hospital Anxiety and Depression Scale (HADS), and a neuropsychological battery (the Trail Making Test [TMT], the Rey Auditory Verbal Learning Test (RAVLT), the

Fig. 1. Study flow chart



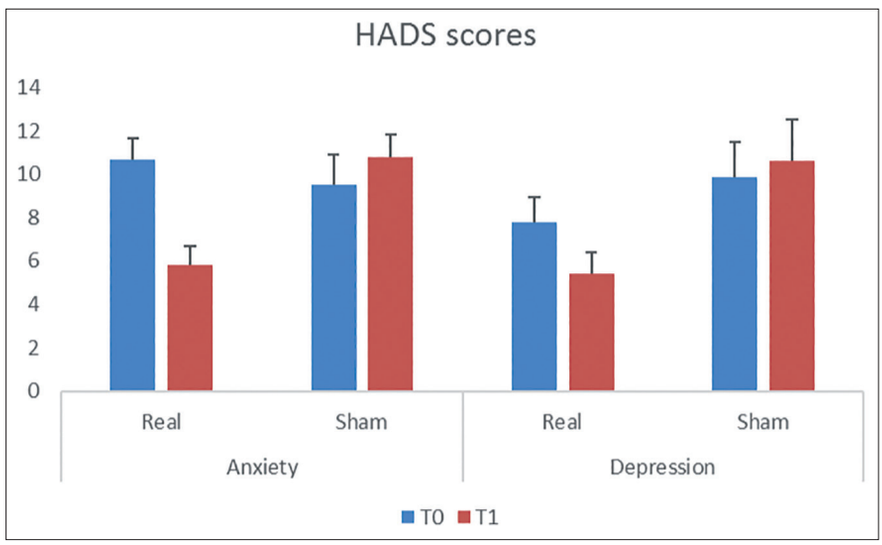


Fig. 2. Mean HADS scores (± SE) in the real and sham tRNS-treated patients at T0 and T1.

Table I. Baseline characteristics of the patients (NS=not significant).

Characteristics (mean values ± SD]	Active tRNS group (n=10)	Sham tRNS group (n=10)	*p*-values
Age, years	41.4 (10.25)	44.2 (9.81)	NS
Duration of FM, years	4.3 (2.62)	5 (5.04)	NS
Concomitant treatment			
Analgesic, % (n)	30% (3)	50% (5)	NS
Antidepressant % (n)	50% (5)	40% (4)	NS
Baseline scores			
VAS pain (0-10 mm)	7.35 (1.79)	8.1 (1.86)	NS
HADS – Anxiety	10.7 (3.02)	9.5 (4.45)	NS
HADS – Depression	7.8 (3.64)	9.9 (5.10)	NS
FIQ	69.21 (16.86)	70.92 (13.88)	NS
TMT A	45.33 (20.49)	65.3 (23.56)	NS
TMT B	110.9 (85.19)	161 (121)	NS
MMSE	28.45 (1.61)	27.24 (1.47)	NS
Forward Digit Span Test	5.13 (0.5)	4.56 (0.7)	NS
Backward Digit Span Test	3.34 (0.66)	3.12 (0.81)	NS
RAVLT part 1	37.09 (7.14)	38.92 (6.03)	NS
RAVLT part 2	7.56 (1.60)	7.88 (2.11)	NS
FAS	25.16 (7.93)	27.79 (10.98)	NS

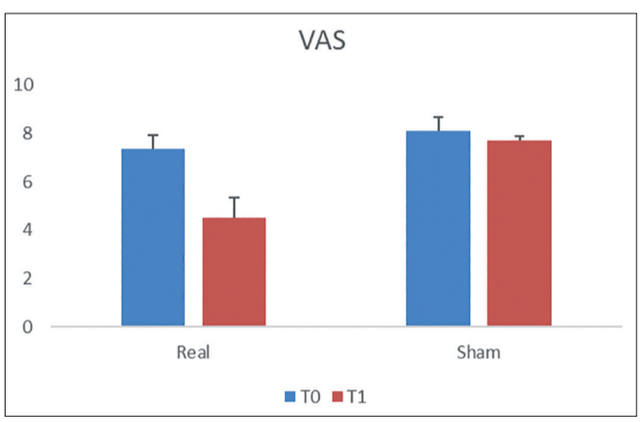


Fig. 3. Mean VAS scores (± SE) in the real and sham tRNS-treated patients at T0 and T1.

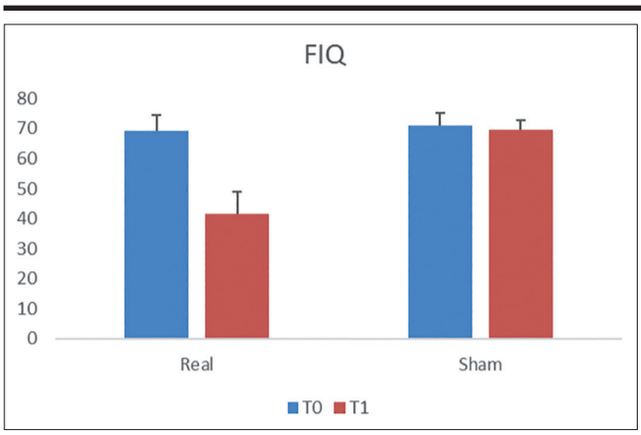


Fig. 4. Mean FIQ scores (± SE) in the real and sham tRNS-treated groups at T0 and T1.

Forward and Backward Digit Span test, and the FAS verbal fluency test.

• *Pain, mood and disability assessment*

The 10-item FIQ was developed to assess the status, progress and outcomes of FM patients (19-21) by measuring the components of health status that are believed to be most affected by FM.

The self-administered VAS was used to rate pain intensity (22). The subjects were asked to place a line perpendicular to the VAS line at the point that best described their pain at the time of completion.

The HADS is a 14-item self-report screening scale that was originally developed as a means of indicating the possible presence of anxiety and depression in the setting of an outpatient clinic (23).

• *Neuropsychological tests*

The TMT provides information concerning visual search, scanning, speed of processing, mental flexibility, and executive functions, and is principally used to explore attentive abilities. It consists of two parts: TMT-A involves drawing a line connecting consecutive numbers from 1 to 25, and TMT-B involves drawing a similar line connecting alternating numbers and letters in sequence (1-A-2-B, and so on). The time to complete each trail is recorded (24).

The Digit Span Test assesses short-term verbal memory span, and the ability to manipulate and update verbal information while it is in temporary storage. The subjects had to listen to a digit span (one digit per second) and then had to repeat it forward (trial 1) or backward (trial 2). The score was equal to the maximum of digits repeated without any error in one of the two trials (25).

The RAVLT is useful for evaluating verbal learning and memory, including proactive inhibition, retroactive inhibition, retention, encoding *versus* retrieval, and subjective organisation (26). Subjects are asked to repeat a given list of 15 unrelated words. The procedure is carried out a total of five times and, after a 20-minute interval, they are asked to recall as many words as possible from the list.

The FAS Verbal Fluency Test (27) is a measure of phonemic word fluency, which is assessed by asking subjects to say as many words as possible beginning with the letters F, A and S within a prescribed time, usually one minute. Verbal fluency is a cognitive function that facilitates the retrieval of stored information, and successful retrieval requires executive control over cognitive process such as selective attention, mental set shifting, internal response generation, and self-monitoring.

Statistical analysis

Analysis of variance (ANOVA) for repeated measures used for each outcome measure, with one between-subject fac-

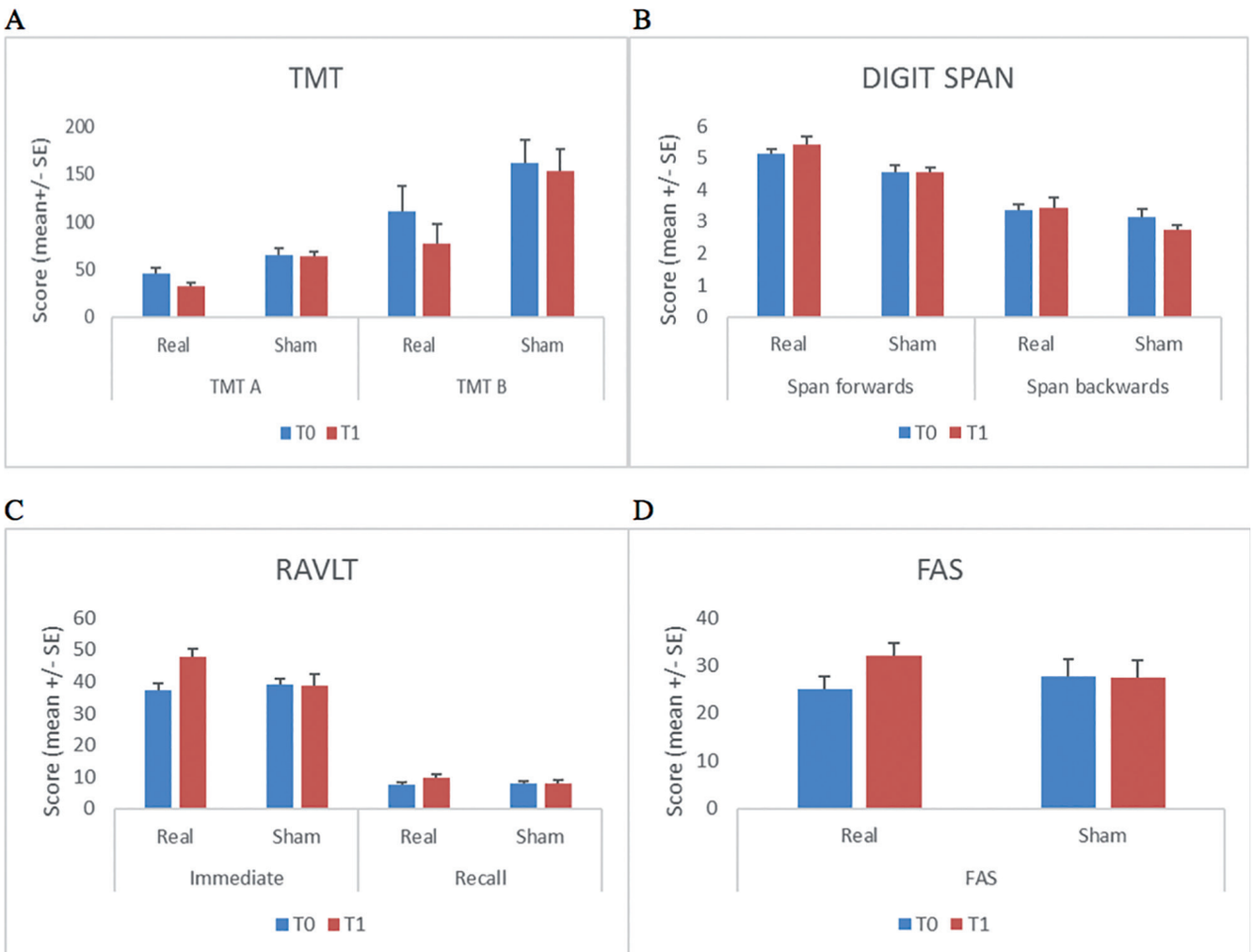


Fig. 5. Mean cognitive test scores (± SE) in the Real and Sham tRNS-treated groups at T0 and T1. **A**: TMT a-b; **B**: Digit span forward and backwards; **C**: RAVLT immediate and recall; **D**: FAS.

tor ("StimType": sham *vs*. real tRNS) and one within-subject factor ("Time": pre- *vs*. post-tRNS, T0 and T1). The significance level was set at $p<0.05$.

Results

Table I shows the socio-demographic variables, clinical characteristics and concomitant treatments of the two groups, which were not significantly different.

Effects of tRNS on pain intensity

ANOVA of the VAS scores showed significant main effects for the factors "StimType" [$F(1, 18)=8.7423$, $p=0.00844$] and "Time" [$F(1, 18)=9.5612$, $p<0.005$], and the interaction "StimType x Time" [$F(1, 18)=5.4335$, $p<0.05$]. Furthermore, real stimulation significantly decreased the VAS score ($p<0.005$), which was significantly lower than that induced by sham stimulation ($p<0.005$).

Effects of tRNS on mood disorders

ANOVA of the anxiety scores showed significant main effects for the factor "Time [$F(1, 18)=4.9215$; $p<0.05$] and the interaction "StimType x Time" [$F(1, 18)=14,597$; $p<0.005$]. The *post hoc* analysis showed that anxiety significantly improved ($p<0.001$) in the group assigned to real rTNS, and the effect was significantly greater than that induced in the sham group ($p=0.023$).

ANOVA of the depression scores showed that the main effect for the interaction "StimType x Time" was only marginally significant [$F(1, 18)=4.4015$; $p=0.05029$]. The *post hoc* analysis showed that depression significantly improved in the real tRNS group ($p<0.05$).

Effects of tRNS on quality of life

ANOVA of the FIQ scores showed significant main effects for the factors "StimType" [$F(1, 18)=4.5575$; $p=0.04678$] and "Time" [$F(1, 18)=32.429$; $p=0.00002$], and the interaction "StimType x Time" [$F(1, 18)=27.267$, $p=0.00006$]. The *post hoc* within- and between-group comparisons of the scores highlighted a significant improvement in the quality of life of the subjects undergoing real tRNS (real T1 *vs*. real T0, $p=0.0002$; real T1 *vs*. sham T1, $p=0.014$).

Effects of tRNS on cognitive impairment (fibrofog)

ANOVA revealed significant main effects for the factors "StimType" (TMT A, TMT B, Forward Digit Span) and "Time" (RAVLT and FAS test), and

for the interaction "StimType x Time" (RAVLT and FAS test). The *post hoc* analysis showed that, in comparison with sham tRNS, active tRNS significantly improved TMT A (p=0.046), RAVLT parts 1 and 2 (p<0.005; p<0.005) and FAS scores (p<0.005), but not TMT B or the Digit Span scores.

Discussion

The aim of this study was to investigate the effects of tRNS of the motor cortex as an alternative therapeutic approach in a group of 20 FM patients, and the results showed that it improved the patients' clinical picture by affecting not only pain, but also the associated mood and cognitive impairments.

The effect was specific as real tRNS lead to significantly greater improvements than sham tRNS. The patients described themselves as feeling more active and proactive: their pain VAS scores were significantly reduced, and the changes in FIQ scores indicated that the treatment decreased the impact of the disease on their quality of life. The decrease in specific HADS scores showed that the treatment had positive effects on mood: it significantly improved anxiety and, a lesser extent, depression. Transcranial RNS also improved the "fibrofog" cognitive dysfunction frequently associated with FM, which mainly involves attention and executive abilities, and greatly contributes to the patients' disability: attention, verbal learning and executive functions were all significantly improved by real tRNS, which lead to a greater increase in TMT, RAVLT and FAS scores than sham stimulation. Finally, tRNS was safe and well tolerated: only one patient reported a slight "hot" sensation during stimulation. Our study had some limitations, including the small number of subjects, the heterogeneity of the FM patients; the lack of a control group, and indeed larger cohorts will be required to validate our findings.

To the best of our knowledge, this is the first study to investigate the use of tRNS in FM, and provides the first evidence that NIBS can have a widespread effect on FM-related dysfunction by improving pain, and affective and cognitive impairments. Previous NIBS studies using anodal tDCS and high-frequency rTMS have only reported its effectiveness on different and separate aspects of the disease that depended on the cortical area targeted by the stimulation: motor cortex activation principally induced pain relief, whereas affective and cognitive symptoms were mainly improved by prefrontal cortex stimulation (14).

Recent studies have found that tRNS has greater facilitatory effects than anodal tDCS and, in some studies, 1 mA tRNS over M1 induced more motor corticospinal excitability than anodal tDCS both during and after stimulation, and thus had greater effects on *motor evoked potentials* even when using the same intensity and duration (15-16). It has also been shown that tRNS improves visual perceptual accuracy (28), and it is more effective than tDCS in increasing visual perceptual learning (29).

It is not clear why tRNS is capable of improving both the pain and other symptoms associated with FM. Unlike tDCS, which uses direct currents at fixed polarity, tRNS and transcranial alternate current stimulation (tACS) are quite new techniques that use alternating currents that change their polarity between electrodes at different frequencies: tACS operates at fixed frequencies, whereas the frequency of tRNS randomly changes within a preset range during the period of stimulation. This random variation of current flow over time can stimulate neurons regardless of their spatial orientation, and overcome the problems caused by the direction of the electric field. It is likely that tRNS cortical modulation is mediated by voltage-dependent sodium channels because the effects are inhibited by carbamazepine, a specific blocker of these channels. The continuous polarisation and depolarisation of the neuronal membrane induced by stimulation can generate a cyclical response, thus reducing the interval between the inhibitory and the excitatory phase, and increasing cortical excitability (30).

Given the particular characteristics of neuronal cell stimulation, another mechanism that probably underlies the wider pleiotropic effects of tRNS on FM is "stochastic resonance", on the basis of which a signal that is too weak to reach a certain threshold can be amplified by adding noise. As a result, tRNS can amplify sub-threshold neural activities, thus increasing the synchronisation of nervous stimuli (28, 31-32). Interestingly, the improved signal-to-noise ratio in the CNS can also lead to increased perception or cognitive performance (33).

In conclusion, on the basis of the findings of this initial study, it seems that the randomly alternating currents of tRNS can globally affect the clinical picture of FM by improving pain and affective and cognitive dysfunctions, thus having a highly positive impact on the patients' quality of life. Given the limited therapeutic resources available for FM, that are in any case usually poorly effective or burdened by side effects, the efficacy and safety of tRNS found in this study suggests that it could become a useful therapeutic option. However, further evidence is required to confirm its effects in larger patient series and establish the most appropriate stimulation parameters for optimising efficacy and maintaining the benefit over time.

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