Brain Stimulation 14 (2021) 51–54

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Transcranial static magnetic field stimulation can modify disease progression in amyotrophic lateral sclerosis

Keywords:
ALS
Brain stimulation
Hyperexcitability
Excitoxicity
Glutamate

Dear Editor,

Glutamate-mediated excitotoxicity is thought to play a pivotal role in the pathogenesis of amyotrophic lateral sclerosis (ALS) [1]. Current pharmacological treatments target glutamatergic neurotransmission, with limited efficacy. Cerebral cortex excitatory transmission can be targeted and modulated using non-invasive brain stimulation techniques such as repetitive transcranial magnetic stimulation (rTMS), with the purpose of antagonizing motor cortical hyper-excitability.

RTMS was tested in several small studies [2], demonstrating a slight reduction of ALS progression related to duration and frequency of treatment. The main limitations of rTMS are that its after-effects are short-lived and that it can be performed only in specialized centers. Other techniques, such as transcranial direct current stimulation (tDCS), can be performed more easily, even under remote supervision at patient's home [3]. Inhibitory tDCS was evaluated in ALS in two studies but the results are controversial [4,5]. Motor cortex stimulation can also be performed invasively using implanted electrodes, and it can be delivered chronically with obvious advantages. Epidural motor cortex stimulation (eMCS) produces physiologic effects that are comparable to those of rTMS [6] and it has been evaluated in a single patient with rapidly progressive ALS: he was implanted in 2006 and he is surprisingly still alive after 14 years [7]. The benefit of eMCS was recently confirmed in a murine model of ALS [8]. Thus, the dose-effect observed in non-invasive studies and the pronounced effect of eMCS both in humans and in animals, suggest that chronic motor cortex stimulation might be effective in slowing ALS progression.

Recently, a new technique of non-invasive transcranial static magnetic field stimulation (tSMS) [9] has been shown to suppress motor cortex excitability of healthy subjects for 10–30 min [9,10]. Since tSMS does not require any electronic equipment, it is easily performed and suitable for daily chronic administration at patients' site.

In this open-label pilot study we evaluated the effects of chronic tSMS in two patients with rapidly progressive non-familial ALS, both taking Riluzole, treated under "compassionate use" authorization (Supplementary material). Moreover, in order to test more directly whether tSMS may reverse cortical hyper-excitability in ALS patients, we assessed the effects of a single tSMS session on cortical excitability.

Disease severity was evaluated using the revised ALS Functional Rating Scale (ALSFRS-R). The first patient, a 50-year-old male, started to present right upper limb weakness in November 2015. At the first evaluation, in July 2017, 13 months before the beginning of stimulation, the ALSFRS-R score was 30. In the following months the patient developed progressive bulbar involvement with dysphagia and in July 2018, because of a respiratory crisis, tracheostomy was performed and ventilation during sleep was started. Because of severe dysphagia, percutaneous endoscopic gastrostomy was also performed at the same time, to ensure nutritional support. TSMS was started in August 2018: at that time, he was tracheotomized and required tube feeding, ALSFRS-R score was 13 (Fig. 1A). The second patient, a 54-year-old female, started to present lower limb weakness in December 2017. At the first evaluation, in October 2018, the ALSFRS-R score was 30. TSMS was started in May 2019: at that time ALSFRS-R score was 17 (Fig. 1A).

In both patients, tSMS was performed daily without any interruption and it is still ongoing. Stimulation was self-administered at patients' home, for 3 times every day at least 4 hours apart; in each session tSMS was applied sequentially for 20 minutes over each motor cortex. TSMS was delivered using a cylindrical Nickel-plated NdFeB magnet of 45 mm diameter with a nominal field strength of ~69 Kg (MAG45r, Neurek, Toledo, Spain), held in place by an ergonomic helmet specifically designed to target the motor cortex (MAGmv1.0, Neurek) (Supplementary material).

Disease monthly progression rate (MPR) was measured as the variation of the ALSFRS-R score over the period of observation. In each patient, we compared MPR before and during stimulation. We also compared disease progression with that of control patients' groups with comparable functional impairment, obtained from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database (Fig. 1B; Supplementary material). Patients were evaluated at least 6 months before treatment and at multiple time points after tSMS beginning, up to 18 months in Patient 1 and up to 9 months in Patient 2.

Both patients and caregivers did not report any difficulty in performing chronic tSMS. Both patients needed a headrest to sustain the helmet during the procedure. No side effects were reported.

Acute effects of tSMS on primary motor cortex (M1) excitability were characterized by a reduction of about 20% of the mean motor

https://doi.org/10.1016/j.brs.2020.11.003

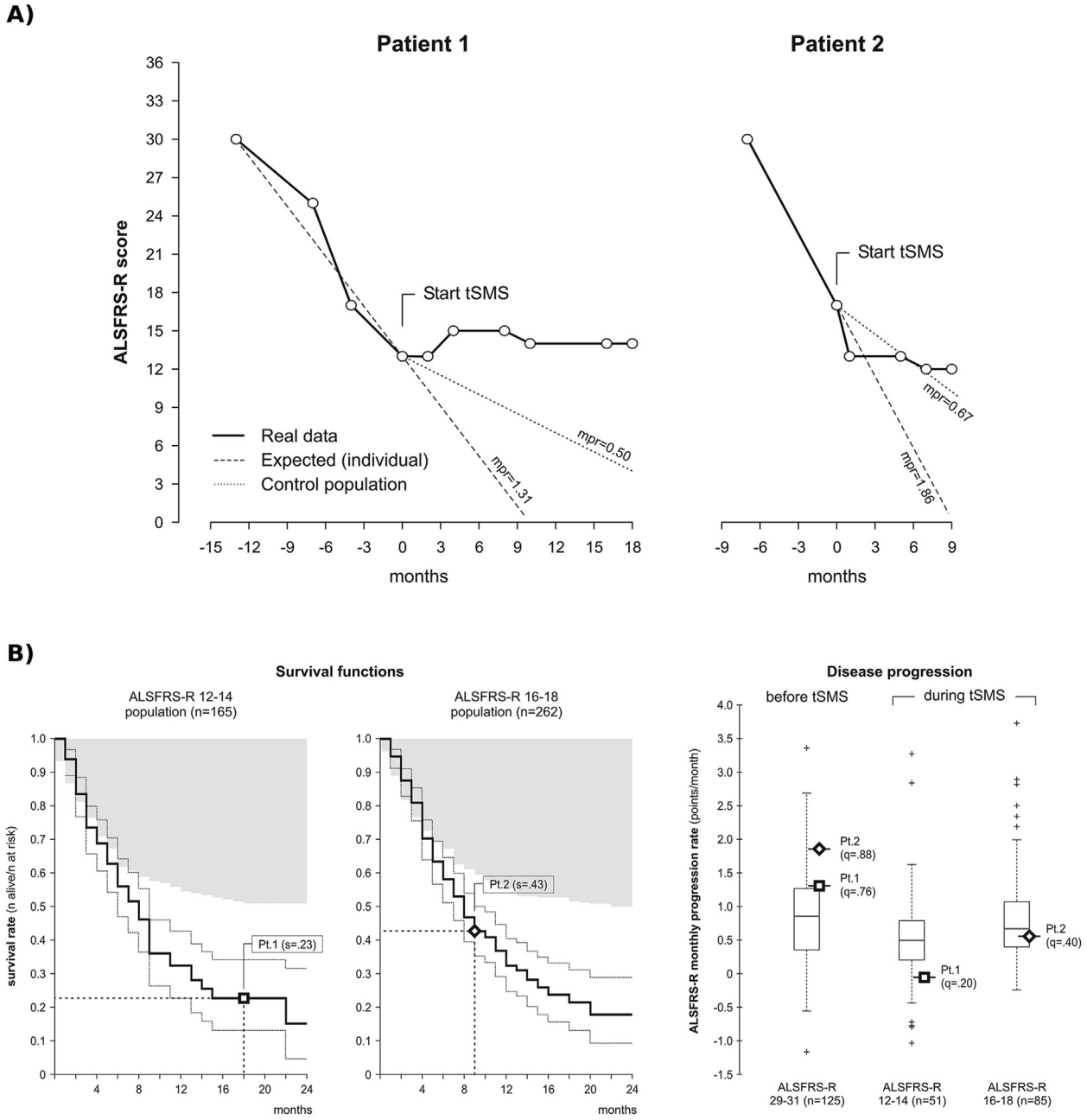

Fig. 1. A) Disease progression as evaluated with the revised ALS Functional Rating Scale (ALSFRS-R). TSMS started at month 0. The dashed line indicates the expected clinical status based on the individual progression before tSMS, assuming a linear worsening of the functional performance. The dotted line indicates disease progression in the control population extracted from the PRO-ACT database (Panel B). The actual clinical status is indicated by the continuous line. mpr: monthly progression rate (points/months). **B) Left panel: survival probability functions** (thick lines) calculated in control samples extracted from the PRO-ACT database, including ALS patients having an initial ALSFRS-R score of 12–14 (control for Patient 1) and of 16–18 (control for Patient 2) and observed for 2 years. Upper and lower bounds of survival curves (thin lines) delimit the 95% confidence interval. Survival rate at each time point is calculated as the ratio between the number of patients alive and the number of patients at risk, i.e. excluding censored patients. Grey bars indicate the proportion of the population that is still under observation at each time point (i.e. initial population minus censored patients). The estimated survival probability at the last time of observation after starting tSMS is 0.23 for Patient 1 and 0.43 for Patient 2. **Right panel: monthly progression rate** of Patients 1 and 2 before and during tSMS, in comparison with that of control samples extracted from the PRO-ACT database with initial ALSFRS-R scores of 29–31, 12–14 and 16–18 (boxplots). Control samples include only patients who were still alive at the end of observation, with a minimum follow-up of 3 months. Boxplots represent the lower quartile, median and upper quartile of the sample distribution; whiskers are set with a maximum length of 1.5 times the interquartile range; + symbols indicate outliers. Patient 1 scores in the upper 25th percentile of its reference group before starting tSMS (i.e. faster progression) and in the lower 20th percentile during tSMS (i.e. slower progression). Patient 2 scores in the upper 13th percentile of its reference group before starting tSMS and in the lower 40th percentile during tSMS.

evoked potential (MEP) amplitude immediately after a 20 min session of right M1 tSMS in *Patient 1* (126 ± 21 (SD) μV at baseline vs 102 ± 15 μV (SD) after tSMS), comparable with the reduction observed in normal subjects [9]. In *Patient 2*, due to pronounced involvement of upper and lower motor neuron, no MEPs could be recorded after stimulation of both motor cortices.

Effects of chronic tSMS on disease progression are reported in Fig. 1.

In *Patient 1,* survival probability at last observation (18 months) is estimated at 0.23, based on the survival function of the control population (Fig. 1B). After the beginning of stimulation, the overall functional status remained stable (MPR reduced to −0.06, in the lower 20th percentile of control population): it was mainly characterized by improvement of swallowing function (not requiring supplemental tube feeding or dietary consistency changes) and loss of functional lower limb movement; the patient continued to require ventilatory support during night only. The overall a priori probability, at the moment of starting tSMS, of surviving and of being in the observed clinical conditions at the last observation can thus be estimated at ~0.05, i.e. 0.23 (survival probability) × 0.20 (probability of MPR ≤ -0.06) (Fig. 1B).

In *Patient 2,* survival probability at last observation (9 months) is estimated at 0.43 (Fig. 1B). After the beginning of stimulation, MPR was reduced to 0.56 (lower 40th percentile of control population), due to slight deterioration of bulbar function and loss of residual lower limb movement. The overall a priori probability of surviving and of being in the observed clinical conditions at the last observation can be estimated at ~0.17, i.e. 0.43 (survival probability) × 0.40 (probability of MPR ≤ 0.56) (Fig. 1B).

In conclusion, we observed a dramatic and prolonged reduction in disease progression in two patients with rapidly progressive ALS treated chronically with tSMS. Patients reported no side effects and at-home self-administered stimulation was considered feasible both by patients and their caregivers.

Considering that our patients had a rapidly progressive form of ALS, the fact that the first patient is still alive and stable, requiring ventilation only during sleep, and has also recovered speech and swallowing functions and that the second patient is also stable and still not tracheotomized suggests a pronounced change in disease course. Comparison with a large control population from the PRO-ACT database indicates that both patients had a low survival probability and a slower disease progression during tSMS than their respective control groups. Of note, we might have even overestimated survival in our 2-year period of analysis since many patients in the PRO-ACT database had a shorter follow-up. The study of motor cortex excitability before and after a single session of tSMS in Patient 1 shows for the first time that it is possible to reduce cortical excitability in ALS with an effect that is comparable to that observed in normal subjects.

Our study has obvious limitations, because only two patients were treated and because we used a historical control group. Nevertheless, present results show that long-term self-administered tSMS is safe and feasible at home and suggest that it has therapeutic potential in ALS. Based on these preliminary observations we have now started a placebo-controlled trial evaluating tSMS as a disease-modifying treatment in ALS (Clinicaltrials.gov: NCT04393467).

Author contributions

V.D., F.R., G.D., F.C. contributed to drafting the text and preparing the figures.

V.D., G.D., F.C., F.R. contributed to the conception and design of the study.

V.D., F.R., G.M., M.B., A.D., F.M. contributed to the acquisition and analysis of data.

Declaration of competing interest

Nothing to report.

Acknowledgments

Part of the data used in the preparation of this article were obtained from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database. As such, the following organizations and individuals within the PRO-ACT Consortium contributed to the design and implementation of the PRO-ACT Database and/or provided data, but did not participate in the analysis of the data or the writing of this report: Neurological Clinical Research Institute, MGH; Northeast ALS Consortium; Novartis; Prize4Life; Regeneron Pharmaceuticals, Inc.; Sanofi; Teva Pharmaceutical Industries, Ltd. We are grateful to the Prize4Life organization and the PRO-ACT Consortium members for making the PRO-ACT Database publicly available.

The “Fondazione ‘Nicola Irti’ per le opere di carità e di cultura”, Rome, Italy, supported present study that is dedicated to the memory of Nicola Irti.

We are extremely grateful to our patients Vincenzo and Nazarena who made this observation possible.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2020.11.003.

References

[1] Eisen A, Braak H, Del Tredici K, Lemon R, Ludolph AC, Kiernan MC. Cortical influences drive amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 2017;88(11):917–24. https://doi.org/10.1136/jnnp-2017-315573.

[2] Edmond EC, Stagg CJ, Turner MR. Therapeutic non-invasive brain stimulation in amyotrophic lateral sclerosis: rationale, methods and experience. J Neurol Neurosurg Psychiatry 2019;90(10):1131–8. https://doi.org/10.1136/jnnp-2018-320213.

[3] Sivaramakrishnan A, Datta A, Bikson M, Madhavan S. Remotely supervised transcranial direct current stimulation: a feasibility study for amyotrophic lateral sclerosis. NeuroRehabilitation 2019;45(3):369–78. https://doi.org/10.3233/NRE-192851.

[4] Benussi A, Alberici A, Cotelli MS, Dell'Era V, Cantoni V, Bonetta E, Manenti R, Filosto M, Morini R, Datta A, Thomas C, Padovani A, Borroni B. Cortico-spinal tDCS in ALS: a randomized, double-blind, sham-controlled trial. Brain Stimul 2019;12(5):1332–4. https://doi.org/10.1016/j.brs.2019.06.011.

[5] Di Lazzaro V, Ranieri F, Capone F, Musumeci G, Dileone M. Direct current motor cortex stimulation for amyotrophic lateral sclerosis: a proof of principle study. Brain Stimul 2013;6(6):969–70. https://doi.org/10.1016/j.brs.2013.06.005.

[6] Di Lazzaro V, Oliviero A, Pilato F, Saturno E, Dileone M, Meglio M, Cioni B, Papacci F, Tonali PA, Rothwell JC. Comparison of descending volleys evoked by transcranial and epidural motor cortex stimulation in a conscious patient with bulbar pain. Clin Neurophysiol 2004;115(4):834–8. https://doi.org/10.1016/j.clinph.2003.11.026.

[7] Di Lazzaro V, Pellegrino G, Capone F, Florio L, Dileone M, Cioni B, Ranieri F. Reduction of disease progression in a patient with amyotrophic lateral sclerosis after several years of epidural motor cortex stimulation. Brain Stimul 2017;10(2):324–5. https://doi.org/10.1016/j.brs.2016.11.012.

[8] Kim H, Kim H-I, Kim Y-H, Kim S-Y, Shin Y-I. An animal study to examine the effects of the bilateral, epidural cortical stimulation on the progression of amyotrophic lateral sclerosis. J NeuroEng Rehabil 2014;11:139. https://doi.org/10.1186/1743-0003-11-139.

[9] Oliviero A, Mordillo-Mateos L, Arias P, Panyavin I, Foffani G, Aguilar J. Transcranial static magnetic field stimulation of the human motor cortex. J Physiol 2011;589(20):4949–58. https://doi.org/10.1113/jphysiol.2011.211953.

[10] Dileone M, Mordillo-Mateos L, Oliviero A, Foffani G. Long-lasting effects of transcranial static magnetic field stimulation on motor cortex excitability. Brain Stimul 2018;11(4):676–88. https://doi.org/10.1016/j.brs.2018.02.005.

Vincenzo Di Lazzaro*, Gabriella Musumeci, Marilisa Boscarino, Alfredo De Liso, Francesco Motolese

Unit of Neurology, Neurophysiology, Neurobiology, Department of Medicine, Università Campus Bio-Medico di Roma, Via Álvaro Del Portillo 21, 00128, Rome, Italy

Giovanni Di Pino
Research Unit of Neurophysiology and Neuroengineering of Human-Technology Interaction (NeXTlab), Università Campus Bio-Medico di Roma, Via Álvaro Del Portillo 21, 00128, Rome, Italy

Fioravante Capone
Unit of Neurology, Neurophysiology, Neurobiology, Department of Medicine, Università Campus Bio-Medico di Roma, Via Álvaro Del Portillo 21, 00128, Rome, Italy

Federico Ranieri
Unit of Neurology, Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, P.le L.A. Scuro 10, 37134, Verona, Italy

* Corresponding author.
E-mail address: v.dilazzaro@unicampus.it (V. Di Lazzaro).

16 October 2020
Available online 10 November 2020