Non-invasive brain stimulation therapy in amyotrophic lateral sclerosis: are we ready for clinical use?

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Despite substantial research efforts, amyotrophic lateral sclerosis remains an incurable neurodegenerative disorder, primarily characterized by the progressive loss of upper and lower motor neurons responsible for voluntary muscle control.[1] Although the precise aetiology of amyotrophic lateral sclerosis is not entirely understood, evidence suggests that excessive glutamatergic stimulation of motor neurons leads to excitotoxicity, significantly contributing to the pathogenesis of the disease.[2]

Riluzole was the first treatment approved for sporadic amyotrophic lateral sclerosis in both Europe and the USA, working by reducing excitotoxicity through inhibition of presynaptic glutamate release and enhancing glutamate uptake, thus protecting motor neurons.[3]

Recently, electroceutical therapies,[4] particularly non-invasive brain stimulation (NIBS), have gained attention as non-pharmacological methods to reduce excitotoxicity by modulating cortical excitability. Techniques like transcranial direct/alternating current stimulation (tDCS/tACS) and transcranial magnetic stimulation (TMS) are prominent.[5] A new technique, transcranial static magnetic stimulation (tSMS), uses neodymium magnets to generate static magnetic fields that suppress cortical excitability.[6] Applied to the motor cortex for 10–30 min, tSMS shows lasting suppression effects,[7] likely due to magnetic torque affecting ion channels. Its portability and simplicity make tSMS a promising candidate for home-based therapy.

In this issue of *The Lancet Regional Health–Europe*, Di Lazzaro and colleagues published the results of a six-month, bicentric, placebo-controlled, randomized, double-blind phase 2 trial investigating tSMS in patients with amyotrophic lateral sclerosis.[8] The trial included 40 participants who were randomly assigned to receive either daily tSMS (n = 21) or placebo stimulation (n = 19). tSMS was self-administered at home, three times per day with at least a 4-h interval between sessions. The primary outcome was the difference in the monthly disease progression rate (MPR), measured by the change in the ALS Functional Rating Scale-Revised (ALSFRS-R) score before treatment initiation and over the six-month treatment period. No significant differences in MPR were observed between the tSMS and placebo groups during either the pre-treatment period (1.02 ± 0.62 vs. 1.02 ± 0.57, p = 1.00) or the treatment period (0.90 ± 0.55 vs. 0.94 ± 0.55, p = 0.83). Secondary endpoints showed that tSMS was safe, well-tolerated, and associated with high compliance, though no significant differences in corticospinal output were detected between the groups. However, the 18-month follow-up revealed a significant improvement in tracheostomy-free survival in the tSMS group compared to the placebo group (Hazard Ratio = 0.27; 95% confidence interval: 0.09–0.80; p = 0.019).

The study concludes that while tSMS did not significantly affect disease progression over the six-month treatment period, the observed long-term survival benefits suggest that further investigation in larger and more extended studies is warranted.

While these findings are encouraging, they must be interpreted cautiously. Several key insights can be drawn from this trial that may inform future research in this area:

1. Safety profile: tSMS was well tolerated, with no evidence of neural damage even after six months of daily 2-h applications. However, the daily usage and the helmet's weight (approximately 2 kg) could pose challenges for patients with significant neck weakness.
2. Delayed clinical benefits: the study observed that the clinical benefits of tSMS, particularly in respiratory function, became apparent during the extended follow-up period, rather than immediately post-application. This aligns with recent trends in amyotrophic lateral sclerosis clinical trials, where the efficacy of treatments is increasingly evaluated over longer observation periods.
3. Mechanistic uncertainties: the precise mechanisms by which tSMS had positive effects on respiratory function, despite targeting the motor cortex area responsible for hand movements, remain unclear. Although tSMS is known to exert localized effects on the targeted cortical region, the possibility of remote effects in connected areas cannot be ruled out, necessitating further research to unravel the specific neural pathways involved.

Given the clinical heterogeneity of amyotrophic lateral sclerosis, a precision medicine approach that targets the most affected cortical regions in individual patients may optimize the therapeutic outcomes of

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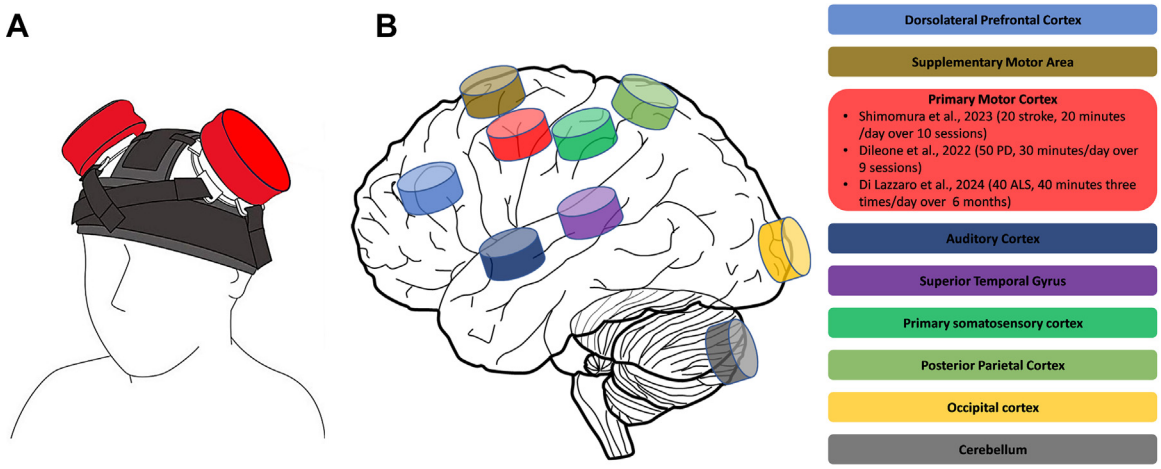

Fig. 1: Schematic representation of transcranial static magnetic stimulation (tSMS) device and overview of stimulated cortical regions. A. Device Illustration: schematic representation of a transcranial static magnetic stimulation (tSMS) device, which consists of high-strength neodymium magnets secured on a cap. The magnets are positioned over specific brain regions (bilateral primary motor cortex) to modulate cortical excitability through the application of a static magnetic field. B. Target Brain Regions: depiction of cortical and subcortical regions of the brain that have been targeted in tSMS studies in preclinical and human studies, encompassing both healthy subjects and patient populations. Each coloured region corresponds to a different area of interest in tSMS research. The red box highlights the primary motor cortex, where tSMS has been investigated for therapeutic purpose in individuals with Parkinson's disease (PD), stroke, and amyotrophic lateral sclerosis (ALS).

neuromodulation therapies like tSMS. Additionally, the lack of objective biomarkers for upper motor neuron dysfunction underscores the urgent need for developing new neurophysiological metrics to better identify patients who may benefit from tSMS. For instance, routine or advanced motor-evoked potentials protocols could provide critical insights into upper motor neuron functionality,[9] potentially serving as biomarkers for patient stratification and therapeutic response evaluation.

Moreover, combining tSMS with other neuromodulation techniques that act at the spinal cord level targeting the lower motor neuron, such as non-invasive spinal cord stimulation,[10] could enhance the overall efficacy of electroceutical interventions in amyotrophic lateral sclerosis.

In conclusion, the findings from this tSMS study pave the way for designing large-scale randomized controlled trials in the field of neuromodulation, potentially broadening the clinical applications of this technique beyond amyotrophic lateral sclerosis to encompass a wide range of neurological and psychiatric disorders characterized by abnormal cortical excitability, such as Alzheimer's disease, epilepsy, Parkinson's disease, schizophrenia, obsessive-compulsive disorder, and stroke (Fig. 1).[8,11–12]

Contributors
Raffaele Dubbioso: Conceptualisation, and writing: original draft, review and editing.
Gianmaria Senerchia: writing: review and editing.

Declaration of interests
None.

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