Effects of Repeated Sessions of Transcranial Direct Current Stimulation on Major Depressive Disorder and Cognition

To the Editor:

We report the following 2 cases to highlight the importance of keeping into account cognitive functioning when assessing the efficacy of transcranial direct current stimulation (tDCS) for the treatment of major depressive disorder (MDD). Major depressive disorder is often associated with mild cognitive impairment (MCI), which further worsens the patient's condition.[1] Anodal tDCS of the left dorsolateral prefrontal cortex (DLPFC) is beginning to demonstrate its efficacy in the treatment of MDD[2] and has potentials for enhancing cognitive functioning in MCI.[3]

We evaluated therapeutic effects of 6 sessions of anodal tDCS of the left DLPFC in two 79-year-old men who were experiencing a 24-month episode of MDD. Patient 1 (P1; 17 years of education) was diagnosed with MCI on prior standard neuropsychological evaluation. Patient 2 (P2; 8 years of education), who had a family history of degenerative diseases, had manifested gait instability for the last 3 years. In this patient, fluorine-18-fluorodeoxyglucose positron emission tomography examination, performed 6 months before, showed reduced bilateral parietotemporal metabolism compatible with Alzheimer disease. Pharmacological treatment (P1: lorazepam 1 mg/die, alprazolam 0.5 mg/die; P2: lorazepam 3 mg/die, quetiapine 300 mg/die, amisulpride 50 mg/die, duloxetine hydrochloride 60 mg/die, zolpidem 20 mg/die) was maintained constant throughout the study.

We also assessed the patients' cognitive functioning and independence on daily activities. Because age-related physiological decline mainly affects right hemisphere functions, and given the evidence that brain stimulation modulates spatial attention,[4] we additionally evaluated tDCS effects on spatial cognition. Patients signed a written informed consent. As in previous studies,[2] tDCS was administered by placing the anode over the F3 site (according to the 10–20 international electroencephalography system) and the cathode (as reference electrode) over the contralateral supraorbital area. Direct current was generated by a Newronika HDCstimulator (Newronika s.r.l.) and delivered via a pair of square scalp electrodes with a surface of 25 cm^2 covered with conductive rubber and saline-soaked synthetic sponges. On the first day, tDCS was applied for only 15 minutes with an intensity of 1 mA. Because patients tolerated well this stimulation duration, for subsequent sessions, tDCS was administrated for 20 minutes at the same intensity. The 6 stimulation sessions were administered every other day over a 2-week period.

The patients' depressive symptoms and quality of life were evaluated on the Hamilton Rating Scale for Depression (HAM-D) and the Short Form Test–36 (SF-36), respectively. The SF-36 is composed of 9 dimensions: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health, changing in health state. The patients' level of independence was rated by the examiner with the help of the caregiver using the Katz Index of Independence in Activities of Daily Living (ADL) and the Lawton-Brody Instrumental Activities of Daily Living Scale (IADL). Cognitive functioning was assessed using the Montreal Cognitive Assessment (MoCA), Verbal Fluency tests (phonemic and semantic), and the Line Bisection Task (LBT; ie, ten 20-cm lines). The above tests were administered 1 week before the stimulation (T0) and 2 weeks after the end of treatment (T3), whereas a brief assessment, consisting exclusively of the LBT and verbal fluency, was administered immediately before (T1) and 2 days after treatment (T2). The HAM-D, SF-36, and ADL and IADL questionnaires were referenced to the last 4 weeks.

Both patients tolerated well tDCS without complications. P1 showed improvement on the HAM-D [T0 = 9 (mild depression); T3 = 6 (no depression)] and on the MoCA [T0 = 20/30 (cognitive decline); T3 = 23/30 (cutoff score)—total MoCA score of 23 or above is considered to be normal]. However, he showed a decrement in 5 of the 9 SF-36 subscales (ie, role-physical, general health, vitality, role-emotional, and mental health). P2 manifested improvement on the HAM-D [T0 = 13 (mild depression); T3 = 6 (no depression)], the ADL [T0 = D (dependent); T3 = A (independent)], and the IADL [T0 = 1/5; T3 = 2/5] questionnaires. Furthermore, he showed amelioration in 2 of 9 SF-36 dimensions (bodily pain and social functioning). However, in this patient, improvement in depression and daily living activities was associated with significant worsening of cognitive functioning as revealed by the MoCA score (from T0 = 20/30 to T3 = 14/30).

Both patients showed a spatial attention rightward bias (about +10 mm or more) on the LBT before (T1: P1 = +9 mm; P2 = +12 mm) and soon after treatment (T2: P1 = +18 mm; P2 = +15 mm) that disappeared at follow-up (T3: P1 = 0 mm; P2 = +4 mm). Only P1 showed some improvement in phonemic fluency at T2 (T0 = 2, T1 = 1, T2 = 4, and T3 = 2), whereas no changes were observed for P2 for the patients' semantic fluency.

These findings are in line with previous studies showing improvement of depression after anodal tDCS of the left DLPFC. Mood improvement was accompanied by improved spatial attention in both patients. However, after treatment, verbal and phonemic fluency showed no (P2) or minimal change (P1), and cognitive functioning (MoCA) improved in 1 patient (P1) and worsened in the other (P2). Worsening of cognitive functioning after tDCS might be explained by the severity and/or the type of the neurocognitive condition of P2 (eg, prefrontal tDCS might have further worsened the activity of the posterior regions). Surprisingly, P1, who showed amelioration in both mood and cognitive scales, manifested a decrement in the quality of life subscales. We hypothesize that the improved cognitive functioning of P1 might have increased awareness of the disease and quality of life.[5] In line with this hypothesis, P2's worsened cognitive functioning might have further impaired awareness of the disease, as revealed by improved evaluations of quality of life. These findings suggest a possible dissociation of tDCS effects on mood and cognition.[2] Future investigations in large groups of patients are needed to understand differential effects of tDCS treatment on depression, cognition,[2] and awareness of symptom amelioration.[5]

Marco Ninghetto, MSc
Roberto Gammeri, MSc
Roberta Miccolis, MSc
SAMBA (SpAtial, Motor & Bodily Awareness) Research Group
Department of Psychology
University of Turin
Turin, Italy

Marcello Nobili, MD
Academy of Medicine of Turin
Turin, Italy

Adriana Salatino, PhD
Raffaella Ricci, PhD
SAMBA (SpAtial, Motor & Bodily Awareness) Research Group
Department of Psychology
University of Turin
Turin, Italy
raffaella.ricci@unito.it

Marco Ninghetto and Roberto Gammeri contributed equally to this work.

The authors have no conflicts of interest or financial disclosures to report.

REFERENCES

1. Ismail Z, Elbayoumi H, Fischer CE, et al. Prevalence of depression in patients with mild cognitive impairment: a systematic review and meta-analysis. *JAMA Psychiat*. 2017;74:58–67.
2. Martin DM, Moffa A, Nikolin S, et al. Cognitive effects of transcranial direct current stimulation treatment in patients with major depressive disorder: an individual patient data meta-analysis of randomised, sham-controlled trials. *Neurosci Biobehav Rev*. 2018;90:137–145.
3. Manenti R, Brambilla M, Benussi A, et al. Mild cognitive impairment in Parkinson's disease is improved by transcranial direct current stimulation combined with physical therapy. *Mov Disord*. 2016;31:715–724.
4. Ricci R, Salatino A, Siebner HR, et al. Normalizing biased spatial attention with parietal rTMS in a patient with focal hand dystonia. *Brain Stimul*. 2014;7:912–914.
5. Salatino A, Momo E, Nobili M, et al. Awareness of symptoms amelioration following low-frequency repetitive transcranial magnetic stimulation in a patient with Tourette syndrome and comorbid obsessive-compulsive disorder. *Brain Stimul*. 2014;7:341–343.