Transcranial Direct Current Stimulation for Autistic Disorder

To the Editor:

Autistic disorder (AD) is a complex neurodevelopmental disorder with an increasing prevalence (1). It has its onset in infancy and is characterized by impairments in multiple behavioral domains, including reciprocal social interaction, language, and variety of interests and activities. Thus far, no specific treatment for AD exists; individual goals may vary among patients and usually include a combination of therapies (2). Despite the existing treatments, AD remains a chronic and a highly disabling condition, causing a considerable economic impact on the community and emotional distress for patients and their families. Thus, new and more effective treatment options are urgently needed.

In the past decade, brain stimulation techniques have yielded promising and encouraging outcomes for the treatment of resistant psychiatric disorders. Among these options, transcranial direct current stimulation (tDCS), a noninvasive, safe, and easy-to-use technique for the focal modulation of cortical brain areas, has recently emerged as an effective and economical tool for treating major psychiatric disorders, such as depression and schizophrenia (3,4). This technique involves the application of spongy electrodes over the scalp, painlessly delivering a weak and direct electrical current to the cerebral cortex. Its therapeutic action has been linked to polarity-dependent neurophysiologic changes in the targeted brain areas, causing either increases (anodal stimulation) or decreases (cathodal stimulation) in cortical excitability (5,6). To the best of our knowledge, tDCS has never been used to treat AD patients. We describe the first case of a patient with AD, who, after undergoing a tDCS course, displayed a dramatic reduction in his behavioral abnormalities.

Mr. P, who was first diagnosed with AD at age 2, is a 26-year old man with an IQ score of 30 on the Leiter International Performance Scale—Revised. He has undergone several psychosocial and pharmacologic interventions to reduce his highly disabling behavior—including risperidone, promazine, pericyazine, lorazepam, and chlordesmethyldiazepam at adequate doses—with no improvement. When tDCS was considered, he was attending an outpatient daily occupational program and undergoing pharmacologic treatment with olanzapine (10 mg/day). Failing to respond to these treatments, he continued to manifest grossly disturbed behavior, including severe irritability, agitation, hyperactivity, and lack of compliance. In some instances, his behavioral outbursts were dangerous. Considering the severity of his symptoms and the failure of other therapies, we administered tDCS after receiving a written informed consent from the patient's parents. Mr. P was subjected to 10 consecutive daily weekday tDCS sessions. Briefly, the cathode was positioned over the left dorsolateral prefrontal cortex (DLPFC), and the anode was placed extracephalically over the contralateral deltoid. A direct current of 1.5 mA was applied for 20 minutes every day. The 25-cm^2 rubber electrodes were wrapped in cotton material, which was moistened with saline to reduce impedance. To assess the behavioral symptoms, we used the Aberrant Behavior Checklist (ABC) before and after the tDCS course. Ratings were based on the direct observation of the patient's behavior as reported by his parents and by the professionals at the rehabilitation center he was attending. Remarkably, Mr. P manifested an overall substantial improvement in his abnormal behaviors, as evidenced by a 40.2% reduction in the total ABC score compared with the basal score (Figure 1). Notably, the clinical improvement was still present at a 3-month follow-up visit, and no adverse effects were reported except for a slight, temporary skin irritation at the site of stimulation.

Our decision to use cathodal stimulation over the left DLPFC was based on recent findings. In particular, converging evidence from neuropathologic, neuropsychologic, and neurophysiologic studies has correlated AD and its behavioral symptoms with deficient neural inhibition in some specific cortical regions, among which the DLPFC (7,8).

In a few studies repetitive transcranial magnetic stimulation, applied over the DLPFC at low inhibitory frequencies, was shown to partially revert neurocognitive deficits and neurophysiologic abnormalities of high-functioning autistic patients (9). Unfortunately, repetitive transcranial magnetic stimulation requires patients to be completely immobilized in a prefixed position for tens of minutes, a condition that is very difficult to achieve in low-functioning and hyperactive patients, who make up the large

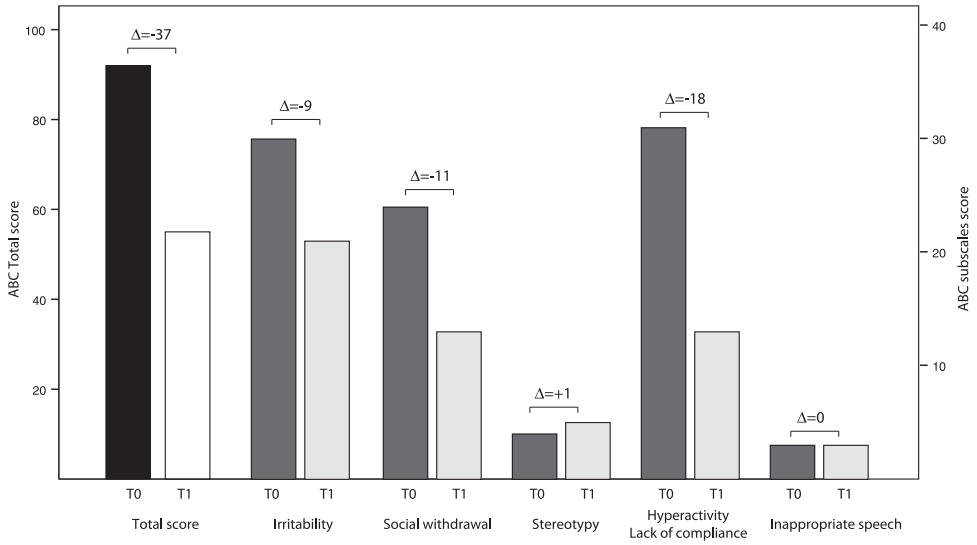

Figure 1. Aberrant Behavior Checklist (ABC) scores before (T0) and after (T1) transcranial direct current stimulation course.

0006-3223/$36.00

majority of the AD population (75%–80%). By contrast, tDCS, thanks to its portability, may be applied to these patients while they move freely and carry out their routine activities.

In the present case study, we performed cathodal inhibitory tDCS targeting the left DLPFC. Our hypothesis was that such application could diminish the neuronal activity in this area while modulating, transsynaptically, the other cortical structures connected with the targeted region. Thus, we speculated that the patient's remarkable behavioral changes were due to the neurophysiologic effects elicited by tDCS over the DLPFC.

The improvement in dysphoria, anxiety, and tantrums, conveyed by a 30% reduction in the ABC subscale for irritability, parallels previous evidence on the beneficial effect of tDCS on depression and anxiety (3,10). Of greater potential impact on rehabilitation programs for patients with AD was the impressive reduction in the ABC subscale scores for social withdrawal (45%) and for hyperactivity and lack of compliance (58%; Figure 1). Indeed, the psychopathologic dimensions considered in these two subscales are more specific to AD and mostly accountable for the poor adherence of AD patients to rehabilitation programs. Consequently, should our results be confirmed, tDCS could provide a crucial support to rehabilitation programs, perhaps by rendering them far more effective than they are today.

However, because the behavioral ratings were partially based on reports of the patient's parents, we cannot rule out that the effects observed might have been biased by the positive expectations from the treatment. Nonetheless, because the behavioral abnormalities of AD patients are usually more manifest when they are not engaged in structured activities, the caregivers' reports are particularly important to estimate the actual impact of a treatment on the lives of patients.

In conclusion, although based on a single case study, these encouraging results ought to inspire more hypothesis-driven research on the effectiveness and viability of tDCS in the treatment of AD and related disorders.

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We thank Professor Giuseppe Miranda, Dr. Gianfranca Auricchio, Dr. Felice Del Genio, Dr. Giuseppina Nappi, Dr. Paola Di Franco, and Mr. Carmelo Fabrizio of the AIAS Center for Neuropsychiatric Rehabilitation of Nola (Naples, Italy) for their collaboration. We also thank Dr. Paola Merolla for her invaluable help editing the manuscript.

All authors contributed substantially to the scientific process leading up to the writing of the correspondence. This is a nonprofit study, and there was no funding source. This study was approved by the local ethics committee (Ethical Committee of the University of Naples Federico II).

Roberta Ferrucci and Alberto Priori are stakeholders of Newronika s.r.l., a spinoff company of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico and of the Università degli Studi di Milano. Carlo Alfredo Altamura has served as a consultant for Roche, Lundbeck, Merck, Astra Zeneca, Bristol-Myers Squibb, Janssen-Cilag, and Otsuka and received fees as a keynote speaker from Sanofi, Eli Lilly, and Pfizer. Silvana Galderisi received fees for educational programs or advisory boards from Amgen Dompé, AstraZeneca, Bristol-Myers Squibb, Eli-Lilly, Otsuka, Innova-Pharma, and Janssen-Cilag. Giordano D'Urso, Dario Bruzzese, Antonio Pascotto, and Carmela Bravaccio report no biomedical financial interests or potential conflicts of interest relevant to the subject matter of the correspondence over the past 2 years, at present, and in the foreseeable future.

1. Dawson G (2012): Dramatic increase in autism prevalence parallels explosion of research into its biology and causes. *Arch Gen Psychiatry* 26:1–2.
2. Myers SM, Johnson CP, American Academy of Pediatrics Council on Children With Disabilities (2007): Management of children with autism spectrum disorders *Pediatrics* 120:1162–1182.
3. Brunoni AR, Valiengo L, Baccaro A, Zanão TA, de Oliveira JF, Goulart A, *et al*. (2013): The sertraline vs. electrical current therapy for treating depression clinical study: Results from a factorial, randomized, controlled trial. *JAMA Psychiatry* 70:383–391.
4. Brunelin J, Mondino M, Gassab L, Haesebaert F, Gaha L, Saud-Chagny MF, *et al*. (2012): Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. *Am J Psychiatry* 169:719–724.
5. Priori A, Berardelli A, Rona S, Accornero N, Manfredi M (1998): Polarization of the human motor cortex through the scalp. *Neuroreport* 9:2257–2260.
6. Nitsche MA, Paulus W (2000): Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol* 527:633–639.
7. Casanova MF, van Kooten I, Switala AE, van England H, Heinsen H, Steinbuch HWM, *et al*. (2006): Abnormalities of cortical minicolumnar organization in the prefrontal lobes of autistic patients. *Clin Neurosci Res* 6:127–133.
8. Enticott PG, Rinehart NJ, Tonge BJ, Bradshaw JL, Fitzgerald PB (2010): A preliminary transcranial magnetic stimulation study of cortical inhibition and excitability in high-functioning autism and Asperger disorder. *Dev Med Child Neurol* 52:179–183.
9. Sokhadze E, Baruth J, Sears L, Sokhadze G, El-Baz A, Casanova M (2012): Prefrontal Neuromodulation Using rTMS Improves Error Monitoring and Correction Function in Autism. *Appl Psychophysiol Biofeedback* 37:91–102.
10. Shiozawa P, Leiva AP, Castro CD, daSilva ME, Cordeiro Q, Fregni F, Brunoni AR (2013): Transcranial direct current stimulation for generalized anxiety disorder: A case study. *Biol Psychiatry* 75:e17–e18.

http://dx.doi.org/10.1016/j.biopsych.2013.11.009