References

Bolognini, N., Pascual-Leone, A., & Fregni, F. (2009). Using non-invasive brain stimulation to augment motor training-induced plasticity. *J. Neuroeng. Rehabil.*, 6, 8.

Bonaiuti, D., Rebasti, L., & Sioli, P. (2007). The constraint induced movement therapy: a systematic review of randomised controlled trials on the adult stroke patients. *Eura Medicophys.*, 43, 139-146.

Fregni, F., & Pascual-Leone, A. (2007). Technology insight: noninvasive brain stimulation in neurology-perspectives on the therapeutic potential of rTMS and tDCS. *Nat. Clin. Pract. Neurol.*, 3, 383-393.

Fugl-Meyer, A.R., Jaasko, L., Leyman, I., Olsson, S., & Steglind, S. (1975). The post-stroke hemiplegic patient, I: a method for evaluation of physical performance. *Scand. J. Rehabil. Med.*, 7, 13-31.

Jebsen, R.H., Taylor, N., Trieschmann, R.B., Trotter, M.J., & Howard, L.A. (1969). An objective and standardized test of hand function. *Arch. Phys. Med. Rehabil.*, 50, 311-319.

Langhorne, P., Coupar, F., & Pollock, A. (2009). Motor recovery after stroke: a systematic review. *Lancet Neurol.*, 8, 741-754.

Liebetanz, D., Nitsche, M.A., Tergau, F., & Paulus, W. (2002). Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain*, 125, 2238-2247.

Mark, V.W., & Taub, E. (2004). Constraint-induced movement therapy for chronic stroke hemiparesis and other disabilities. *Restor. Neurol. Neurosci.*, 22, 317-336.

Nitsche, M.A., Cohen, L.G., Wassermann, E.M., Priori, A., Lang, N., Antal, A., et al. (2008). Transcranial direct current stimulation: state of the art 2008. *Brain Stimul.*, 1, 206-223.

Rioult-Pedotti, M.S., Friedman, D., & Donoghue, J.P. (2000). Learning-induced LTP in neocortex. *Science*, 290, 533-536.

Williams, J.A., Imamura, M., & Fregni, F. (2009). Updates on the use of non-invasive brain stimulation in physical and rehabilitation medicine. *J. Rehabil. Med.*, 41, 305-311.

Wittenberg, G.F., & Schaechter, J.D. (2009). The neural basis of constraint-induced movement therapy. *Curr. Opin. Neurol.*, 22 (6), 582-588.

Brain stimulation in Alzheimer disease

Maria Cotelli [1] - Rosa Manenti [1] - Sandra Rosini [1]
Michela Brambilla [1] - Orazio Zanetti [1] - Carlo Miniussi [1, 2]

[1] *IRCCS San Giovanni di Dio Fatebenefratelli, Brescia, Italy*

[2] *Department of Biomedical Sciences and Biotechnologies, National Neuroscience Institute, University of Brescia, Brescia, Italy*

mcotelli@fatebenefratelli.it

Keywords: Neurodegenerative diseases; tDCS; rTMS

Recent studies have reported enhanced performance on specific cognitive tasks in patients with several types of neurological disease, after receiving non invasive brain stimulation (BS), i.e., repetitive Transcranial Magnetic Stimulation (rTMS) or transcranial Direct Current Stimulation (tDCS) to specific cortical areas (Miniussi et al., 2008). Regarding rTMS, in the language domain, facilitation effects have been reported following online stimulation of the left or right prefrontal cortex (PFC). Specifically, this procedure has been shown to reduce vocal reaction times for picture naming in normal subjects (Cappa et al., 2002) and to improve the number of correct responses in Alzheimer Disease patients affected with mild to moderate (Cotelli et al., 2006b) and moderate to severe (Cotelli et al., 2008) stages. In addition, persistent beneficial effects of off-line rTMS on sentence comprehension in Alzheimer (AD) patients have been recently described (Cotelli et al., 2010). These facilitati61on effects seem related to the possibility of inducing changes in cortical excitability and therefore reorganization of a functional network from which cognitive performance may benefit. Moreover, regarding aphasia patients, recent studies reported that the administration of rhythmic rTMS to the anterior portion of the right homologue of Broca's area results in improvements in the ability to name pictures in patients with non-fluent aphasia (Naeser et al., 2010).

Another BS technique that can be tested in these kinds of studies is tDCS. The recently revived technique of tDCS involves applying weak electrical currents directly to the head, over a long period of time, usually in

the order of minutes (~5-30 min). Behavioral facilitatory effects have been highlighted with regard to implicit motor learning (Nitsche et al., 2003; Reis et al., 2009), working memory (Fregni et al., 2005), pitch memory (Vines et al., 2006), perception (Antal et al., 2004) and language (Fertonani et al., 2010). tDCS has been shown to be able to induce modifications of the cortical excitability and behavior which may outlast the stimulation period itself. Given this potential, there is currently a growing interest in applying these methodologies therapeutically, to reduce cognitive deficits in patients with chronic neurodegenerative diseases.

Using tDCS in eight patients with chronic, non fluent, post stroke aphasia Monti and coauthors (Monti et al., 2008) reported naming facilitation when the patients receive cathodal stimulation over the damaged left frontotemporal areas. Moreover, an interesting study of combined treatments was conducted by Baker and coauthors (Baker et al., 2010). The study revealed significantly improved naming accuracy of treated items after anodal tDCS compared with sham tDCS. In addition, the treatment effect persisted at least 1 week after treatment.

In the present pilot study fourteen AD patients were randomly assigned to one of two study groups. The first group underwent a 4-week of real tDCS stimulation protocol, while the second one underwent a 2-week placebo treatment, followed by 2 weeks of real tDCS stimulation. Both the patients and the examiners were blind to the group assignment in order to reduce confounding placebo effects. The assessment included a standard cognitive assessment and an experimental testing. The cognitive assessment included tests to screen for dementia (Folstein et al., 1975) together with neuropsychological tests for memory, praxia abilities, reasoning, executive functions and language. All the tests were administered and scored according to standard procedures (Lezak et al., 2004). The experimental evaluation assessed action and object naming abilities as reported also in previous studies (Cotelli et al., 2006a).

Regarding the pilot results described in the present report the researchers do not know yet the experimental group associated to each patient and the unique available follow up for the present report is at 12 weeks (assessed for 11 patients out of the 14 included patients). Accordingly, the behavioral effects induced by the tDCS protocol were assessed using a repeated measures ANOVA, considering time (baseline, 4 and 12 weeks) as a within-subject factor. A significant effect of the time of the assessment was found in Mini Mental State Examination (MMSE) ($F(2, 20) = 3.47$, $p = 0.05$), experimental action naming ($F(2, 20) = 3.26$, $p = 0.06$), action naming subtest of the Battery for the Analysis of Aphasic Deficits, BADA ($F(2, 20) = 3.83$, $p = 0.04$) and nouns naming subtest of the Aachener Aphasie Test, AAT ($F(2, 20) = 3.70$, $p = 0.04$). Post hoc comparisons showed that in all the five measures the

performance was higher at the end of the treatment than at baseline and no significant changes were shown from the end of the treatment and the follow up at 12 weeks.

The present preliminary results suggest once more the possible effect of BS applied to left PFC on cognitive performance of AD patients.

References

Antal, A., Nitsche, M.A., Kruse, W., Kincses, T.Z., Hoffmann, K.P., & Paulus, W. (2004). Direct current stimulation over V5 enhances visuomotor coordination by improving motion perception in humans. *J. Cogn. Neurosci.*, 16, 521-527.

Baker, J.M., Rorden, C., & Fridriksson, J. (2010). Using transcranial direct-current stimulation to treat stroke patients with aphasia. *Stroke*, 41, 1229-1236.

Cappa, S.F., Sandrini, M., Rossini, P.M., Sosta, K., & Miniussi, C. (2002). The role of the left frontal lobe in action naming: rTMS evidence. *Neurology*, 59, 720-723.

Cotelli, M., Borroni, B., Manenti, R., Alberici, A., Calabria, M., Agosti, C., et al. (2006a). Action and object naming in frontotemporal dementia, progressive supranuclear palsy, and corticobasal degeneration. *Neuropsychology*, 20, 558-565.

Cotelli, M., Calabria, M., Manenti, R., Rosini, S., Zanetti, O., Cappa, S.F., & Miniussi, C. (2010). Improved language performance in Alzheimer disease following brain stimulation. *J. Neurol. Neurosurg. Psychiatry*.

Cotelli, M., Manenti, R., Cappa, S.F., Geroldi, C., Zanetti, O., Rossini, P.M., & Miniussi, C. (2006b). Effect of transcranial magnetic stimulation on action naming in patients with Alzheimer disease. *Arch. Neurol.*, 63, 1602-1604.

Cotelli, M., Manenti, R., Cappa, S.F., Zanetti, O., & Miniussi, C. (2008). Transcranial magnetic stimulation improves naming in Alzheimer disease patients at different stages of cognitive decline. *Eur. J. Neurol.*, 15, 1286-1292.

Fertonani, A., Rosini, S., Cotelli, M., Rossini, P.M., & Miniussi, C. (2010). Naming facilitation induced by transcranial direct current stimulation. *Behav. Brain Res.*, 208, 311-318.

Folstein, M.F., Folstein, S.E., & McHugh, P.R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.*, 12, 189-198.

Fregni, F., Boggio, P.S., Nitsche, M., Bermpohl, F., Antal, A., Feredoes, E., et al. (2005). Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. *Exp. Brain Res.*, 166, 23-30.

Lezak, M., Howieson, D., & Loring, D.W. (2004). *Neuropsychological Assessment (fourth ed.)*. Oxford: University Press.

Miniussi, C., Cappa, S.F., Cohen, L.G., Floel, A., Fregni, F., Nitsche, M.A., et al. (2008). Efficacy of repetitive transcranial magnetic stimulation / transcranial direct current stimulation in cognitive neurorehabilitation. *Brain Stimul.*, 1, 326-336.

Monti, A., Cogiamanian, F., Marceglia, S., Ferrucci, R., Mameli, F., Mrakic-Sposta, S., et al. (2008). Improved naming after transcranial direct current stimulation in aphasia. *J. Neurol. Neurosurg. Psychiatry*, 79, 451-453.

Naeser, M.A., Martin, P.I., Treglia, E., Ho, M., Kaplan, E., Bashir, S., et al. (2010). Research with rTMS in the treatment of aphasia. *Restor. Neurol. Neurosci.*, 28, 511-529.

Nitsche, M.A., Schauenburg, A., Lang, N., Liebetanz, D., Exner, C., Paulus, W., & Tergau, F. (2003). Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. *J. Cogn. Neurosci.*, 15, 619-626.

Reis, J., Schambra, H.M., Cohen, L.G., Buch, E.R., Fritsch, B., Zarahn, E., et al. (2009). Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. *Proc. Natl. Acad. Sci. USA*, 106, 1590-1595.

Vines, B.W., Schnider, N.M., & Schlaug, G. (2006). Testing for causality with transcranial direct current stimulation: pitch memory and the left supramarginal gyrus. *Neuroreport*, 17, 1047-1050.

Transcranial direct current stimulation (t-DCS) in neuropsychiatric disorders

Adelio Lucca - Alessia Malaguti - David Rossini
Raffaella Zanardi - Giulia Paredi - Fausto Panigada
Adele Pirovano - Cristina Colombo - Enrico Smeraldi

San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Clinical Neurosciences Department, Milano, Italy

lucca.adelio@hsr.it

Keywords: transcranial Direct Current Stimulation; Depression; Vascular disease; MODA

Transcranial direct current stimulation (t-DCS) is a non invasive and safe method to stimulate cerebral cortex with two scalp electrodes, anode and cathode. The technique was established in 1950s-1960s primarily in animals. Early studies showed that the exposure to sub-threshold direct current stimulation induced acute and long-lasting effects on neuronal activity: an increased neuronal activity with the anode placed on the scalp and a reduced neuronal activity with the cathodal polarity (Bindman et al., 1964). These results have been replicated in humans in recent years (Nitsche et al., 2000). Moreover, it has been shown that t-DCS influences cerebral blood flow, in particular anodal stimulation increases regional cerebral blood flow in many cortical and subcortical regions compared to cathodal and sham stimulation (Lang et al., 2005).

In neurological clinic t-DCS has been tested on cognitive/behavioural dysfunctions, such as stroke, Parkinson Disease and pain. In psychiatric clinic, the t-DCS has been investigated only in the treatment of depression, unlike transcranial magnetic stimulation (TMS), that has been used for different psychiatric disorders, like Obsessive Compulsive Disorders and alcohol or cocaine craving.