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Letter to the Editor

Targeting negative symptoms in schizophrenia: Results from a proof-of-concept trial assessing prefrontal anodic tDCS protocol☆

Dear Editors,

To date, only one trial assessed transcranial direct current stimulation (tDCS) for the treatment of schizophrenia (Brunelin et al., 2012). Thirty schizophrenic patients with persistent auditory hallucinations were randomized to receive either active stimulation or sham. tDCS was applied twice daily for 5 days. The authors showed an improvement of hallucinatory symptoms (primary endpoint) after the end of stimulation, with sustained clinical response during follow-up.

Following this first trial, we performed a phase II, open-label, proof-of-concept trial assessing the clinical efficacy of anodic tDCS for negative symptoms in schizophrenia. All were diagnosed with schizophrenia and were under pharmacotherapy. Recruitment occurred in a university day-care psychiatric center. Elected patients underwent a 10-day tDCS protocol consisting of consecutive tDCS sessions over a two-week period. Computer modeling was implemented as to target tDCS action over the prefrontal cortex and subcortical structures related to negative symptoms in schizophrenia following previous analyses (Bikson et al., 2012). The anode was located over the left dorsolateral prefrontal cortex and cathode was positioned over the contralateral deltoid area. We used a direct current of 2.0 mA for 20 min.

A total of nine patients were elected for the study. The mean age was 40.33 (±9.4), six males. All were diagnosed with schizophrenia and were under pharmacotherapy. Baseline psychotic symptoms were assessed by the PANSS with a mean overall score of 83.44 points (±5.41). Regarding PANSS sub-analysis, baseline positive dimension had a mean of 15.77 (±1.71), negative symptoms dimension had a mean of 28.44 (±4.63) and general dimension had a mean of 39.22 (±1.39). Considering depressive symptoms as assessed by Calgary Inventory, patients presented with a mean baseline score of 1.88 (±1.36) — in fact, no patient presenting with depression was elected to participate in the study. Regarding cognitive symptoms, patients presented a mean score of 21 (±4.35) at MoCA.

Regarding primary outcome, patients presented with significant amelioration of negative symptoms with a mean reduction of 6.77 points (±2.48) in comparison to baseline scores (t = 8.16; df:8; $p < 0.00001$). Exploratory analysis demonstrated a significant overall reduction in PANSS (mean reduction of 7 points ±1.85; t = 3.77; df:8; $p < 0.00001$) following negative symptoms reduction. No significant changes were observed for either positive or general dimensions in PANSS (respectively, t = 0.75; $p = 0.471$ and t = 0.81; $p = 0.440$). Considering depressive symptoms, no significant changes from baseline were observed (t = 0.96; $p = 0.844$). We found no clinical or demographical variables to be confounders regarding main outcome (Table 1).

Neuroimaging studies have been pointed towards an association between schizophrenia and gray matter reductions in the prefrontal cortex (Fraguas et al., 2014) (Pasternak et al., 2015). In fact, even during rest hypoactivity of the prefrontal cortex is observed (Ellison-Wright and Bullmore, 2009). Same results highlighting prefrontal hypoactivity have arisen from transcranial magnetic stimulation (TMS) trials showing that high-frequency rTMS (excitatory) was effective in the treatment of negative symptoms (Prikryl et al., 2013).

In the present study anodic tDCS protocol was found to ameliorate negative symptoms in schizophrenia. The present results need to be taken as hypothesis-driven given the study design. Limitations to this study include its unblinded nature, small sample size, lack of a control group, and short length. Moreover, our results may be overestimated due to intrinsic characteristics such as the placebo effect and Hawthorne effect. However, the current "proof-of-concept" trial is aimed at evaluating preliminary effects of a new experimental tDCS protocol. We understand that the trends seen in the completers shall strongly justify a larger double-blind study with better estimation of sample size.

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Dr. Milton Kurimori reported no biomedical financial interests or potential conflicts of interest.

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Dr. Marom Bikson has equity in Soterix Medical Inc. and the City University of New York has patents on brain stimulation with MB as inventor.

Mohamed Aboseria reported no biomedical financial interests or potential conflicts of interest.

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Contributors

Dr. Milton Kurimori participated in the present article with recruitment and assessment, his participation contributed significantly to the work.

Dr. Pedro Shiozawa participated in the present article with data analysis, his participation contributed significantly to the work.

Dr. Marom Bikson participated in the present article with data analysis, his participation contributed significantly to the work.

Table 1
Overview of main outcome and exploratory analysis for clinical data between baseline and after stimulation protocol.

Variable	Mean difference	Sd	p	t	df	95% IC
PANSS	7.00	1.85	0.005	3.77	8	2.720 11.279
Positive dimension	0.33	1.32	0.471	0.75	8	−1.350 0.683
Negative dimension	6.77	2.48	<0.00001	8.16	8	4.864 8.690
General dimension	1.66	6.16	0.440	0.81	8	−3.071 6.405
Baseline Calgary	0.11	2.47	0.844	0.96	8	−1.789 2.011
Baseline MoCA	2.44	1.85	0.222	1.32	8	−1.819 6.708

PANSS: Positive and Negative Symptoms Scale; Calgary: for depressive symptoms assessment in schizophrenia; MoCA: Montreal Cognitive Assessment; Sd: standard deviation; t: *t*-test; df: degrees of freedom; IC: confidence interval.

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Mohamed Aboseria participated in the present article with data analysis, his participation contributed significantly to the work.

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Conflict of interests

Dr. Milton Kurimori reported no biomedical financial interests or potential conflicts of interest.

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