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LETTER TO THE EDITOR

Non-invasive brain stimulation for the treatment of the negative symptoms in Schizophrenia: results from an updated systematic review and a meta-analysis

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Dears Editors,

Negative symptoms in Schizophrenia consist of affective flattening, anhedonia, avolition, asociality, and avolition. These symptoms are the main predictors of functional outcomes resulting in poorer social and occupational functioning, in particular for patients with a young age of onset of the disorder¹. Antipsychotic treatment evolved in the last five decades reaching a significant control over positive symptoms but still yield small to no effect results for negative symptoms²⁻⁴. Non-invasive brain stimulation (NIBS) techniques emerged as an alternative to standard pharmacological treatment options.

The developments in functional neuroimaging and biomarkers enabled the better understanding of the cortical and subcortical areas involved in the negative symptoms of schizophrenia. The idea of modulating such dysfunctional areas in a controlled, focused way, in contrast to electroconvulsive therapy, enabled the rise of the NIBS field of study. This area comprehends the transcranial magnetic stimulation (TMS)^{5,6} and the transcranial direct current stimulation (tDCS)⁷. These techniques have been proved efficacious for neuroplasticity enhancement, boosting treatment response

for refractory symptoms in different neurological and psychiatric disorders^{8,9}. Although promising results have been previously reported on the effect of TMS and tDCS for negative symptoms in schizophrenia¹⁰, they are still controversial⁸. With the purpose of gathering the knowledge on the randomized controlled trials on NIBS for negative symptoms in schizophrenia, we conducted a systematic review and meta-analysis. We hypothesize that NIBS techniques are superior to sham stimulation for treatment of this symptom domain.

Our systematic review yielded 440 studies after duplicates were removed. In the end, 31 studies complied with inclusion criteria and were selected for the quantitative analysis (1272 patients). Studies sample sizes ranged from 11 to 157 subjects, with mean ages of 38.8 years (SD = 7.27) and 39.93 years (SD = 7.75) for the sham and active groups, respectively.

Quality assessment revealed that all studies were properly randomized, sham-controlled, with patient and evaluator blinded. Also, all studies scored at least 4 in the Jadad scale¹¹.

As our primary outcome we found that active NIBS was significantly superior to sham NIBS calculating the effect size for the endpoint ($g = 0.23$; 95% CI 0.11 – 0.34). In general, heterogeneity was low and not significant in

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our analysis ($I^2=2.3\%$, $p=0.429$ for the χ^2 test) and the Egger's test was not significant ($p=0.179$).

In accordance with previous meta-analytical studies that reported positive results using TMS and tDCS for the

treatment of patients with psychiatric disorders^{9,12-14}, we present compelling positive findings that encourage the perpetuation of the effort to find a way to the successful treatment of negative symptoms in schizophrenia.

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