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Dorsolateral Prefrontal Repetitive Transcranial Magnetic Stimulation in Pediatric Sample with Autism Spectrum Disorder

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ABSTRACT

ASD is a neurodevelopmental disorder, characterized by social and communication difficulties, repetitive behaviors, sensory issues and cognitive delays. ASD is diagnosed clinically, based on behavioral symptoms and unfortunately currently exists no cure. Transcranial magnetic stimulation TMS is a noninvasive method for cortical excitability modulation that may aid to physiology and therapeutic prospects. TMS acts on synapse level to obtain balance between glutamate mediated excitation and GABA mediated inhibition for optimal level of neuroplasticity. This is a single blinded sham controlled interventional study assessing therapeutic effect of repetitive TMS in patients with ASD during the period from September 2016 to February 2017, throughout this period patients received active and sham intervention of rTMS over 12 weeks. Participants recruited from rehabilitation units at the Institute of Psychiatry, Ain Shams University, Cairo, Egypt, included 30 patients aged from 4 to 10 years old (26 males, 4 females) diagnosed ASD as defined in DSM-5 with mild to moderate severity by Childhood Autistic Rating Scale CARS. Fifteen participants received active rTMS intervention over left and right Dorsolateral Prefrontal Cortex and 15 received sham interventions to assess the Placebo effect. After sessions documented follow up notes of any side effects or clinical findings. Study results showed after intervention, significant differences in eye to eye contact, relating to people, emotional reciprocity, verbal and nonverbal communication, restricted interests, adaptation to change, stereotypy, while increase in activity level and irritability in 21% and no change in 50% of active group compared to non-change in sham group.

Keywords: ASD, Transcranial Magnetic Stimulation, DLPFC, intracortical inhibition, plasticity

INTRODUCTION

Autism Spectrum Disorder ASD is heterogeneous neurodevelopmental disorders with genetic and neurobiological etiology and epigenetic factors. Linked mutations involving several genes supporting synaptic maturation, stabilization, plasticity, neuronal migration and dendritic development. Symptoms of ASD develop in the first years of life when synaptic development and maturation are occurring rapidly in frontal and temporal cortices (8) which affect cognition and behavior.

The goal of pharmacotherapy for ASD children is to alleviate symptoms. Risperidone and aripiprazole have been approved by Federal Drug Administration FDA for the treatment of irritability, aggression, self-injurious behavior and mood swings. Also, in open-label studies, levetiracetam and divalproex sodium appeared to be well tolerated and successful. Unfortunately, there are no medications treat cognitive impairment which may help children to maximize benefits of educational and behavioral therapy.

Noninvasive brain stimulation is neurophysiological technique including transcranial magnetic stimulation TMS and transcranial direct current stimulation tDCS. Introduced approximately 25 years ago, by using inter-stimulus interval technique TMS may modulate NMDA dependent Hebbian plasticity of the corticospinal tracts (46). tDCS increased language production and its electrophysiology, as well as in treatment of numerous neurological and psychiatric illnesses. Their mechanisms of action are not fully understood; appears producing changes in the activity of neurons of stimulated motor cortex which can be measured as motor evoked potentials by electromyography (EMG). Single and paired pulse TMS protocols used exclusively for investigational purposes, rTMS paradigms-theta-burst stimulation (TBS) and paired associative stimulation (PAS) in assessment of ASD neuroplasticity.

rTMS Frontal lobe stimulation (20 Hz) induced marked increase of dopamine in hippocampus. rTMS on left dorsolateral prefrontal cortex DLPC (20 Hz) caused reduction in raclopride (Dopamine Receptors) of caudate nucleus, affect glutamate in right DLPC and left cingulate cortex, while 10 Hz stimulation modulate tryptophan/5-HT metabolism in limbic areas. Theoretically, these effects on dopaminergic system may induce beneficial effects on parkinsonian, neurodevelopmental, psychiatric disorders and fronto-parietal circuits abnormalities.

Based on the autism theories, candidate genes are involved in synaptic development and plasticity so aberrant mechanisms of plasticity can be modified by using TMS for long term potentiation and depression-like plasticity. Application of low-frequency (0.5 -1 Hz) stimulation to dorsomedial prefrontal cortex, DLPFC, pars triangularis and pars opercularis and Supplementary Motor Area lead to normalization in event-related potentials (ERPs) of visual processing in a selective attention task, induced gamma frequency (EEG) activity over frontal and parietal sites and reduction in repetitive-ritualistic behavior, irritability language processing, social relating and self-oriented anxiety during emotional situations to no changes in sham condition. TMS is considered quite safe if applied within current safety guidelines; however, should screen patients before TMS and promising cooling techniques, active and passive cooling methods is presented in.

With a large number of different solar PV modules cooling techniques employed, there is a lack of criteria for the effectivity assessment of the cooling systems. In some publications, the gained power is considered without taking into consideration the surface area of the PV cells. In publication a new approach for photovoltaic module cooling technique evaluation using the

temperature-dependent photovoltaic power and the reference power ratio measured at standard test conditions is suggested. In other publications, the total increase in efficiency is measured. This makes it impossible to compare the cooling methods and to assess the application reasonability of the cooling systems and the gained benefit of each employed system. Thus there is a need for a universal value or criterion to assess the effectivity of the given cooling method and technique.

METHOD AND MATERIALS:

This study is single blinded sham controlled interventional was conducted at the Institute of Psychiatry, Ain Shams University, Egypt and participants recruited from the rehabilitation unit by simple random sampling. It included 30 patients (26 males, 4 females), age (4 to 10 years old), were randomly assigned in two groups (active intervention: n = 15; Sham Intervention: n = 15). Clinical diagnosis as ASD was confirmed by an independent psychiatrist according to The Structured Clinical Interview for DSM-5 criteria. Mild to moderate severity of ASD measured by Child Autism Rating Scale CARS.

ETHICAL CONSIDERATIONS:

•The research protocol was accepted by the research ethics committee and the scientific research committee of Faculty of Medicine, Ain Shams University.

•An informed written consent signed by guardians of the participants. It contained name of the study, aim of the study, detailed description of the procedure, expected benefits and side effects. Also, they have the right to withdraw from the study at any time without justification. Moreover, they were informed that this study could be used for scientific publication without disclosure of their personal identity.

•All participants underwent physical, neurological examination and EEG at baseline to exclude contraindication conditions.
Data analysis: collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 20). Descriptive statistics as Mean, Standard deviation (± SD), Median and Interquartile range (IQR), Student T Test, Chi-Square, Fisher's exact, also paired t-test, Wilcoxon signed rank test.

RESULT

I. DESCRIPTIVE DATA:
Demographic characteristics of study participants: both groups were matched regarding age and gender. No significant differences between both groups in family history of neurological, psychiatric and medical illness. There are no significant differences between both groups in Developmental milestones.

Illness characteristics before rTMS intervention: These symptoms were examined by Childhood Autism Rating Scale (CARS) for follow up. Upon comparing the active and sham group before intervention using the symptomatology profile there was no statistically significant difference between the two groups confirming proper randomization. All the cases of both groups were moderately impaired in the domain of adaptation to change, statistically difference significant only in the body use / stereotype.

II: ANALYTICAL DATA OF THE STUDY

After finishing 12 sessions of active rTMS and sham technique for the two groups results showed that significant difference improvement and reduction of symptoms severity of all items except for activity level and irritability. Sham group patients showed no significant differences except for imitation and obeying order.

POST rTMS ASSESSMENT SCALES

After finishing 12 sessions of active rTMS and Sham technique for the two groups results of comparing both groups in the assessing scales, a paired t test was performed for each group separately to assess the improvement of each group. The active group CARS mean improved from 33.93±1.7 to 30.57 ±1.9, in the Vineland mean from 63.7±10.9 to 67.4±10.2, and in the ATEC score improved dramatically from 100.2±17.9 to 55.5±15.8 (these improvements were highly significant). The overall difference in the improvement between the two groups was assessed by repeated measure ANOVA model where all assessing scales showed highly statistically significant difference between the groups.

DISCUSSION

rTMS may represent a novel strategy for reducing core and associated ASD symptoms. Current study participants younger in age depending on brain plasticity theory "attempts to intervene earlier has better response". Most studies published till 2016 participants were older age (13-33 years). A systematic review on TMS neurophysiology in motor cortex, using motor-evoked potentials (MEPs) and short interval intracortical inhibition (SICI) on ASD patients and controls, and average age were (101 individuals, 22.1 ± 8.8 yrs) and controls (83 individuals, 23.3 ± 6.9 yrs) (26). In similar studies, age of participants (12-27 years), (9-27 years). Using narrower age range, in the current study made groups homogenous, thus alleviating the age factor difference that may contribute to different response to rTMS.

This study aimed to assess tolerability and potential therapeutic effect of rTMS in 30 ASD patients, 15 received active rTMS and 15 received sham intervention (placebo effect). Study targeted DLPFC as it was hypothesized that using rTMS on DLPFC might improve core symptoms, due to its extensive network connections with other specialized distributed and local networks in the brain, DLPFC also selected in 90% of prior studies and rTMS used for prefrontal stimulation in different psychiatric and neurological disorders.