EFFECT OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN PATIENTS WITH AUTISM SPECTRUM DISORDER

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ABSTRACT

Background: *The autism spectrum disorders (ASD) describes a range of conditions classified as neurodevelopmental disorders. ASD is one of the most common child psychiatric disorders. The mechanisms underlying this brain disorder are still unknown.*

Objective: *To study the therapeutic effect of repetitive Transcranial Magnetic Stimulation (rTMS) in patient diagnosed with autism spectrum disorder (ASD).*

Patients and Methods: *the sample consisted of 30 patients selected from outpatient pediatric clinic of Sayed Galal Al-Azhar University Hospital; in the period from June 2020 to December 2020 divided into two groups (15 received active rTMS intervention and 15 received Sham interventions to assess the Placebo effect). And their ages ranged from 4 to 10 years old diagnosed with ASD by using a modified clinical sheet, designed to diagnose of ASD according to DSM-5 criteria and Assessment of severity of ASD using Child Autism Rating Scale (CARS), Assessment of response and effectiveness of the treatment using Autism Treatment Evaluation Checklist (ATEC), Vineland Adaptive Behavior Scale (VABS) measure IQ and level of functioning, Clinician-Rated Severity of Autism Spectrum and Social Communication Disorders.*

Results: *The results of the study after the completion of 12 sessions of rTMS, There was significant decrease in the ASD severity according to CARS and DSM clinical rated severity and significant improvement in ATEC scores in the active group patients while non-significant changes in the sham group patients, while by Vineland scores showed no significant difference that in the active group patients as well as in the sham group.*

Conclusion: *this study concluded that rTMS over left dorso-lateral prefrontal cortex may be safe and effective way of providing a relief of ASD symptoms.*

INTRODUCTION

Autism spectrum disorders (ASDs) are complex neurodevelopmental disorders characterized by qualitative impairments in three domains: social interaction, communication, and repetitive stereotyped behavior.

ASD is a new Diagnostic and Statistical Manual of Mental Disorders DSM-5 disorder encompassing the previous DSM-IV autistic disorder (autism), Asperger's disorder, childhood disintegrative disorder, Rett's disorder, and pervasive developmental disorder not otherwise specified. It is characterized by deficits in two core domains:

Deficits in social communication and social interaction, restricted repetitive patterns of behavior, interests, and activities **(American Psychiatric Association, 2013)**.

ASD is one of the most common child psychiatric disorders, with a prevalence estimated at 1.1% of the population **(Centers for Disease Control and Prevention, 2012)**. The pathogenesis of ASD is still unknown. A major obstacle is that autism seems to have several etiologies. and it is likely that a combination of multiple genetic and environmental factors could result in ASD Studies showed an increase in prevalence associated with lower Socioeconomic status of parents **(Rai et al., 2012)**, Sub mission date: 15 February 2021.

In addition, 60–90% of monozygotic twins are concordant for autism spectrum disorder, compared with about 10% for dizygotic twins **(Hallmayer et al., 2011)**. ASD is diagnosed clinically, based on observation and assessments of behavior using Diagnostic and Statistical Manual of Mental Disorders (DSM) **(Ameis and Catani, 2015)**.

ASD is a chronic condition that requires a comprehensive treatment approach. Management must be individualized according to the child's age and specific needs **(Maglione et al., 2012)**.

The importance of early intensive behavioral and educational interventions in improving outcomes for children with ASD is well documented **(Volkmar et al., 2014)** Complementary medicine is typically defined as nontraditional treatments that are used together with conventional medicine **(Akins et al., 2010)**. Pharmacologic therapy for children with ASD is directed mainly towards the treatment of the associated psychiatric or behavioral symptoms that interfere with learning, socialization, health, safety, quality of life, or overall functioning **(Volkmar et al., 2014)**.

Combined pharmacologic and non-pharmacologic interventions may be more beneficial than

medication alone **(Aman et al., 2009** and **Frazier, 2012)**.

One way that may be accomplished is with transcranial magnetic stimulation (TMS), a noninvasive method for cortical excitability modulation that aid in ASD diagnosis and therapeutic prospects as well **(Oberman et al., 2015)**.

A TMS device generates a strong magnetic field, inducing an electric current in a specific area, and this in turn induces intracerebral currents in associated neural circuits **(Ruhe et al., 2012)**.

TMS mechanism of action at the synaptic level the fine balance between excitation mediated by glutamate and inhibition mediated by GABA could be crucial for optimal level of neuroplasticity **(Baroncelli et al., 2011)**.

Studies that used rTMS for therapeutic purposes to improve either symptoms or physiological and cognitive indices have focused on four areas of ASD brain: the dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (mPFC) supplementary motor area, and right pars triangularis and pars opercularis **(Oberman et al., 2014)**.

About rTMS safety data available indicate that when it is applied within established safety guidelines, is well tolerated and safe in both adult and pediatric ASD populations **(Oberman et al., 2015)**.

Aims of the Work

To study the therapeutic effect of repetitive Transcranial Magnetic Stimulation (rTMS) in patient diagnosed with autism spectrum disorder (ASD)

PATIENTS AND METHODS

Ethical considerations:

1. Consents were taken from parents/ caregiver to participate in the study.
2. Approval of ethical committee in the department, college and university were obtained before the study.
3. No conflict of interest and fund from any source.
4. The patient has the right to withdraw from the study.
5. The data of the study are confidential and the patient has the right to keep it.
6. The author declined that there is no conflict of interest regarding the study or publication.

Inclusion Criteria including:

1. Autism cases (ages 4-10 years) diagnosed according to the criteria of DSM-5.
2. Both males and females included.
3. No recent changes in the drug treatment and rehabilitation over the period of intervention.
4. Mild to moderate severity of autism spectrum disorder measured by CARS.

Exclusion criteria:

1. Past history of seizures.
2. Past history of other neurological disorder.
3 Presence of other comorbid psychiatric disorders.

This Single blinded Sham controlled interventional (clinical trial) study was conducted at Sayed Galal University Hospital on 30 children who were chosen randomly from those who attending the pediatric outpatient clinic , The age of the patients ranged from 4 to 10 years old They were diagnosed clinically according to Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5) through a designed semi structured interview and through application of Childhood Autistic Rating Scale (CARS). Participants were divided into two groups by simple random method 15 well receive active rTMS intervention (group-I) and 15 receive Sham intervention to assess the Placebo effect (group-II).

Participants were asked to continue their medications and behavioral treatment regimens throughout the duration of the study.

All patients included in the study were subjected to the following procedures:

Baseline assessment before Application of rTMS : Semi-structured Interview and Clinical Examinations By using a modified clinical sheet, designed to diagnose of ASD according to DSM-5 criteria, Assessment of severity of ASD using Child Autism Rating Scale (CARS), Assessment of response and effectiveness of the treatment using Autism Treatment Evaluation Checklist (ATEC), Vineland Adaptive Behavior Scale (VABS) measure IQ and level of functioning, Clinician-Rated Severity of Autism Spectrum and Social Communication Disorders.

Application of transcranial magnetic stimulation: rTMS was administered weekly for 12 weeks at psychiatric department Sayed Galal University Hospital with the 1st six sessions over the left dorso-lateral prefrontal cortex (DLPFC), whereas the remaining six

treatments over the right dorso-lateral prefrontal cortex (DLPFC) at low frequency 1 Hz and intensity 90% of motor threshold (15 trains x 10 sec, 150 pulse per session at 26 sec interval) every week for total 12 consecutive weeks.

Sham stimulation conducted to (group-II) patient to exclude the placebo effect by using the figure of 8 coils and producing same recorded noise simulating the active session.

Reassessment of patient After Application of 12 sessions of TMS: By using Child. Autism Rating Scale (CARS). Using Autism. Treatment Evaluation Checklist (ATEC). Vineland Adaptive Behavior Scale (VABS) Clinician-Rated Severity of Autism Spectrum and Social Communication Disorders.

Statistical analysis:

The collected data was revised, coded, tabulated and introduced to a PC using statistical package for social science (SPSS 20) using t-test. P-value is considered significant > 0.05.

RESULTS

Table (1): Socio- Demographic Data

		Total no. = 30
Age	Mean ± SD Range	6.57 ± 1.74 4 – 10
Sex	Male Female	27 (90.0%) 3 (10.0%)
Age of mothers	Mean ± SD	31.73 ± 4.83
	Range	22 – 40
Age of fathers	Mean ± SD	34.90 ± 5.48
	Range	24 – 46
Consanguinity	No	22 (73.3%)
	Yes	8 (26.7%)
History of neurological illness	No	27 (90.0%)
	Yes	3 (10.0%)
History of psychiatric illness	No	29 (96.7%)
	Yes	1 (3.3%)
History of ASD	No	29 (96.7%)
	Yes	1 (3.3%)
History of developmental delay	No	24 (80.0%)
	Yes	6 (20.0%)
History of medical illness	No	27 (90.0%)
	Yes	3 (10.0%)

This table shows Socio- Demographic Data of the studied cases.

Table (2): Comparing CARS* before and after the application of rTMS among group-I

CARS		Group-I		Test value	P-value	Sig.
		Before rTMS	After rTMS			
General impression	Normal	1 (6.7%)	4 (26.7%)	16.441	0.001	HS
	Mild	2 (13.3%)	10 (66.7%)			
	Moderate	12 (80.0%)	1 (6.7%)			
	Severe	0 (0.0%)	0 (0.0%)			
Total score of CARS	Mean ± SD	38.20 ± 4.48	29.27 ± 3.41	18.897	0.000	HS
	Range	28 – 44	21 – 33			

CARS: Childhood Autistic Rating Scale

Upon comparison of group-I patients before and after the intervention, results showed significant decrease in severity of CARS.

Table (3): Comparing CARS before and after the application of rTMS among group-II

CARS		Group-II		Test value	P-value	Sig.
		Before rTMS	After rTMS			
General impression	Normal	1 (6.7%)	1 (6.7%)	0.373	0.946	NS
	Mild	2 (13.3%)	1 (6.7%)			
	Moderate	12 (80.0%)	13 (86.7%)			
	Severe	0 (0.0%)	0 (0.0%)			
Total score of CARS	Mean ± SD	38.63 ± 4.26	36.23 ± 3.78	0.264	0.157	NS
	Range	29.5 – 44	28.5 – 40			

In the group-II comparing before and after placebo intervention there was no significant decrease in severity of CARS.

Table (4): Comparing DSM5 level of severity of ASD before and after the application of rTMS among group-II

		Group-II		Test value	P-value	Sig.
		Before rTMS	After rTMS			
Severity of social communication by DSM5	**Normal**	0 (0.0%)	0 (0.0%)	0.370	0.946	NS
	Mild	2 (13.3%)	1 (6.7%)			
	Moderate	13 (86.7%)	14 (93.3%)			
	Severe	0 (0.0%)	0 (0.0%)			
Severity of restricted nterest and repetitive behavior by DSM5	**Normal**	0 (0.0%)	0 (0.0%)	0.000	1.000	NS
	Mild	1 (6.7%)	1 (6.7%)			
	Moderate	14 (93.3%)	14 (93.3%)			
	Severe	0 (0.0%)	0 (0.0%)			

These table show insignificant deference between before and after intervention.

Table (5): Comparing DSM5 level of severity of ASD before and after the intervention among group-I

		Group-I		Test value	P-value	Sig.
		Before rMST	After rTMS			
Severity of social communication by DSM5	**Normal**	0 (0.0%)	3 (20.0%)	16.971	0.001	HS
	Mild	3 (20.0%)	11 (73.3%)			
	Moderate	9 (60.0%)	1 (6.7%)			
	Severe	3 (20.0%)	0 (0.0%)			
Severity of restricted interest and repetitive behavior by DSM5	**Normal**	0 (0.0%)	1 (6.7%)	26.267	0.000	HS
	Mild	1 (6.7%)	14 (93.3%)			
	Moderate	14 (93.3%)	0 (0.0%)			
	Severe	0 (0.0%)	0 (0.0%)			

These table show that there is highly improvement after intervention regarding severity of social communication and restricted interest by DSM5 in group-I.

Table (6): Difference between Vineland and ATEC before and after application of rTMS among (group I) and (group II)

Variable		Before	After	Paired T test P	RM ANOVA P
Vineland	**Group 1**	63.71±10.9	67.43±10.2	0.000 HS	0.000 HS
	Group 2	67±13.6	67.43±13.3	0.08 NS	
ATEC	**Group 1**	100.21±17.9	55.5±15.8	0.000 HS	0.000 HS
	Group 2	97.36±12.5	90.07±11.03	0.000 HS	

These table show significant difference before and after intervention in (group I) regarding Vineland and ATEC while in (group II) there is significant difference in ATEC and insignificant difference in Vinland.

DISCUSSION

The current study aimed to study the potential therapeutic effect of rTMS in 30 patients diagnosed with ASD, 15 received active rTMS intervention and 15 received sham intervention to assess its placebo effect. In the current study, the age of participating children (N=30) ranged from 4-10 years old, mean age of around ± 6. It was hypothesized that using rTMS on some brain areas - namely this study has chosen Dorso Lateral Pre Frontal Cortex (DLPFC) - might improve core symptoms of autism spectrum disorder (ASD). In this study comparing between active and sham group patients before starting the intervention and after finishing 12 sessions, DSM5 severity levels by Clinician-Rated Severity of Autism Spectrum and Social Communication Disorders **(American Psychiatric Association, 2013)**, and assessment scales CARS Childhood Autism rating Scale for diagnosis and severity, Vineland Scale IQ for functioning and ATEC (Autism treatment Evaluation Checklist) for treatment evaluation. The DLPFC was chosen due to its extensive network connections with other specialized distributed and local networks in the brain which is not specific to one side **(Casanova, et al., 2015)**, and thus current study targeted both left and right DLPFC similar to **(Baruth et al., 2010**; **Casanova et al., 2012** and **Sokhadze et al., 2012)** while **(Sokhadze et al., 2009** and **Sokhadze et al., 2010)** targeted left DLPC only Selecting 1 Hz as

the stimulation frequency as studies have shown that low-frequency rTMS (≤1Hz) increases inhibition of stimulated cortex **(Maeda et al., 2000)** there is also a lower risk for seizures the lower the rTMS frequency.

The current study answered the question aimed to study whether rTMS has potential therapeutic effect or not effective in treatment core symptoms of ASD.

By comparing DSM5 level of severity of the two main domains of ASD after the intervention between active and Sham group it was found that there was significant improvement among active group patients 15\15(100%) decreased severity in social communication domain from severe to moderate1\15(6.7%) and from moderate to mild 11/15 (73.3%) and 3\15(20.0%) turned near normal as reported from their care givers and observed clinically, while in sham group patients there was no change in the level of severity of the two domains of ASD.

In the assessing scales described before showed that significant difference between the two groups in active group patients after intervention mean point of CARS improved from moderate to mild severity and from 38.20 decreased to be 29.27, while in the Sham group patients the mean value remaining nearly the same as 38.

As regards follow up of symptoms after intervention by ATEC comparing the two group's results showed significant improvement in the active group patients the mean value decreased from 100 to be 55 while in the Sham group patients decreased from 97 to 90.

As regards IQ Vineland scores no significant difference that in the active group patients means near the same value 63.5 to 67.4 and also in the sham group no change in the value of 67.

Casanova et al., used similar TMS protocol typical to our study and showed that there was a significant difference between groups in reduction of repetitive and restricted behavior patterns following 12 sessions of bilateral rTMS as measured by the Repetitive Behavior Scale (RBS). There was also a statistically significant group differences in reduction in irritability as measured by the Aberrant Behavior Checklist (ABC). The waiting-list group showed no significant changes in repetitive behavior, irritability, social awareness, or hyperactivity as a result of the waiting period.

Sokhadze et al. showed similar results following rTMS, subjects were reported to have reduced repetitive-ritualistic behavior as measured by the Repetitive Behavior Scale; but no changes in social awareness, and irritability, or hyperactivity were observed. The TMS treatment course was administered two times per week for 3 weeks (a total of six 0.5 Hz rTMS treatments, 150 pulses per session) over the left DLPFC only. In the current study the used rTMS protocol was more extensive of weekly sessions for 12 weeks That better results were seen in **(Sokhadze et al., 2010)** than that were our study.

Repetitive Behavior Scale: Revised (RBS), Total RBS-R score decreased from 23.4 to 19.1 Total RBS-R score decreased in **(Sokhadze et al., 2014)** and from 25 to 18 in **(Sokhadze et al., 2010)**.

Other studies **(Sokhadze et al., 2010**; **Sokhadze et al., 2014** and **Casanova et al., 2014)**. All had full-scale IQ >80 assessed as inclusion just before intervention using the Wechsler Intelligence Scale for Children, Fourth Edition.

CONCLUSION

This study concluded that repeated sessions of TMS over left and right DLPFC have the potential to become an important therapeutic tool in ASD treatment and has shown significant benefits in treating core symptoms of ASD.

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تأثير الحث المغناطيسي المتكرر عبر الجمجمة في المرضى الذين يعانون من اضطراب طيف التوحد

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الهدف من الدراسة: دراسة التاثير العلاجي المحتمل للتنبيه المغناطيسي المتكرر عبر الدماغ على مرضى اضطراب طيف التوحد.

المرضي وطرق العلاج: تكونت العينة من 30 مريضًا تم احتيارهم من العيادة الخارجية للاطفال مستشفى سيد جلال الجامعي مقسمة إلى مجموعتين (15 تلقوا تدخلاً نشطًا لـ rTMS و15 تلقوا تدخل وهمي لتقييم تأثير الدواء الوهمي) وتراوحت أعمارهم من 4 إلى 10 سنوات تم تشخيصهم باضطراب طيف التوحد ASD باستخدام ورقة سريرية معدلة، مصممة لتشخيص ASD وفقًا لمعايير DSM-5 وتقييم شدة ASD باستخدام مقياس تصنيف التوحد عند الأطفال (CARS). درجة الخطورة حسب تقييم الطبيب وفقًا لـ DSM-5. قائمة مراجعة تقييم علاج التوحد (ATEC) مقياس فينلاند للسلوك التكيفي (VABS) وذلك للفتره من اول يونيو 2020 حتى نهاية ديسمبر 2020.

النتائج: نتائج الدراسة بعد الانتهاء من 12 جلسة من rTMS، كان هناك انخفاض كبير في الشدة من قبل CARS و DSM تصنيف الشدة السريرية وتحسن كبير في درجات ATEC في

مجموعة المرضى النشطين عند مقارنة التغييرات غير الهامة في الشام مجموعة المرضى، بينما أظهرت نتائج Vineland عدم وجود فرق كبير عن المرضى في المجموعة النشطة وكذلك في المجموعة الصورية.

الخلاصة: أن التحفيز المغناطيسي المتكرر عبر الجمجمة على قشرة الفص الجبهي الظهرية الجانبية اليسرى قد يكون طريقة آمنة وفعالة للتخفيف من أعراض اضطراب طيف التوحد.