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Repetitive Transcranial Magnetic Stimulation of the Dorsomedial Prefrontal Cortex in a group of adolescents with Attention Deficit/Hyperactive Disorder: Preliminary Report.

Open Access **Research Article**

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Abstract

Background

Treatment of Attention Deficit Hyperactivity Disorder (ADHD) during adolescence is often problematic, because patients either reject it or are refractory to drugs. Repetitive Transcranial Magnetic Stimulation (rTMS) is a noninvasive brain stimulation technique, which represents an alternative for those adolescents with ADHD who reject pharmacological treatment or who do not improve their symptoms with it.

Objective

To explore the clinical utility of rTMS at high-frequency (5 Hz), applied through a double cone coil (DCC) on the Dorsomedial prefrontal cortex (dmPFC), both for active and sham stimulation, in a group of adolescents drug-free and with methylfenidate (MTP) treatment.

Subjects and methods

Twenty-eight male adolescents with ADHD (13-18 years old) were evaluated using clinimetric tests (CEAL-ADHD and DU-PAUL), before, during and at the end of the rTMS. Two groups without MTP treatment (n = 9 each) were integrated: rTMS 5Hz (ACTIVE) and rTMS SHAM. From these, patients with severe symptoms on both scales were selected to compare with those who were under treatment with MTP: [rTMS 5Hz, rTMS SHAM), 5Hz + MTP, 1Hz + MTP]. All received a total of 15 rTMS sessions (ACTIVE or SHAM).

Results

The rTMS of the mdPFC in the different groups that received it (rTMS 5Hz without MTP, 5Hz+MTP, 1Hz+MTP) significantly improved ADHD symptoms compared to rTMS SHAM group.

Conclusions

This study is the first to explore the effects of rTMS using a DCC on mdPFC in ADHD; finding a greater benefit in those adolescents (with and without pharmacological treatment) who presented symptoms considered severe.

Keywords: Adolescents; ADHD; rTMS; dmPFC; Methylphenidate

Introduction

Adolescence is the stage of development that occurs between childhood and adulthood and is characterized by the beginning of puberty as well as particular neurobiological, cognitive, and social development. This period becomes critical for the development of significant psychopathologies, worsening disorders that were already present, and a transient increase in mortality rates due to risk-taking behavior *[1]*. Attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in childhood, and their symptoms may continue through adolescence and into adulthood. ADHD is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity. Information related to these symptoms generally comes from parents and teachers *[2,3]*. These core symptoms, particularly when they are associated with comorbidities, affect not only the perception of the patient's quality of life but also add burden to the family for their care. Parents of adolescents with ADHD, for example, may have to deal with academic problems, difficulties for socialization, tendency to use substances and to develop other risky behaviors *[4]*. Meta-analyses based on functional magnetic resonance imaging (fMRI) studies have shown several impairments in ADHD patients involving right and left hemispheric dorsal, ventral, and medial fronto-cingulo-striato-thalamic and fronto-parieto-cerebellar networks that mediate cognitive control, attention, timing and working memory, among other functions *[5]*. Therefore, the appropriate treatment of ADHD becomes particularly important in children and adolescents. The current evidence establishes that it should be multimodal (pharmacological and psychosocial) and take into

account not only the patient's ages but also the associated comorbidities *(see [2] for details)*. The use of stimulant medications has resulted effective in reducing ADHD's core symptoms for most adolescents *[6]*. Methylphenidate (MTA) is considered the first choice of pharmacological treatment, but it has been reported that approximately 20% of ADHD patients do not obtain benefits with this drug *[7]*. Other reports indicate that a significant group of MPA-treated patients never achieve complete symptomatic remission; either due to poor response to treatment, loss of effectiveness after long periods (resistance), or due to drug intolerance and adverse effects *[8,9]*.

Repetitive Transcranial Magnetic Stimulation (rTMS) is a noninvasive brain stimulation technique, which represents an alternative for those adolescents with ADHD who reject pharmacological treatment or who do not improve their symptoms with it. rTMS have been used in the treatment of several disorders in children and adolescents (e.g. ADHD, autism, Tourette syndrome, depression, and schizophrenia), trying to alleviate their symptoms modulating cortical excitability. In addition, rTMS over the prefrontal cortex is a potential target to influence the activity of the D4 dopamine receptor in ADHD. However, safety is quite important in pediatric research; therefore, it is recommended to use the appropriate stimulation protocols to make rTMS a tolerable technique and with minimal side effects *[10-12]*. Recently, a group of European experts updated the recommendations on the therapeutic efficacy of rTMS *[13]*. In their opinion, only one original sham-controlled study *[14]* deserved to be mentioned in ADHD section, but unfortunately, it included only 22 adults with ADHD (9 real, 13 shams) and did not result in any clinical benefit. Reports on rTMS and ADHD are scarce in the pediatric population, and all stimulation protocols involve the dorsolateral prefrontal cortex (DLPFC), right or left, and high or low-frequency rTMS (≥5Hz or ≤1Hz) *[15-21]*. The most frequent references were that of Weaver et al. *[22]* and that of Gómez et al. *[23]*. Although there are more recent references *[24,25]*, there is still no consensus on which is the appropriate protocol (coil and stimulation variables) to improve ADHD symptoms. On the other hand, it has been emphasized that the impairment of the functioning of the dorsal anterior cingulate cortex (dACC) and anterior insula is associated with deficiencies in the self-regulation of emotions, thoughts, and behaviors that are a hallmark of psychiatric illness *[26]*. RTMS using a double cone coil (DCC) has been shown to modulate the neural activity in the dACC by placing the coil over the dorsomedial prefrontal cortex (|dmPFC) *[27]*. Stimulation over the dmPFC, as indeed on ACC, has been proven to be safe. It is possible to find reviews on the benefits derived from this type of treatment concerning the symptoms in psychiatric disorders *[28,29]*. Among the psychiatric illnesses that have shown encouraging results with deep transcranial magnetic stimulation are Major Depressive Disorder (MDD) *[30-32]* and Obsessive-Compulsive Disorder (OCD) *[33,34]*. Therefore, as some authors have highlighted the clinical and neurobiological link between OCD and ADHD *[35,36]*, then rTMS applied over the dmPFC could be safe and useful to improve the symptoms in ADHD adolescents. Our purpose was to explore in a special period of development, e.g. adolescence, the clinical utility of rTMS at a more tolerable high-frequency (5 Hz), applied through a DCC on the dmPFC, both for active and sham stimulation, in a group of adolescents drug-free and with MTA treatment.

Materials and Methods

Protocol Criteria

The inclusion criteria were: male, adolescents, 13 to 18 years old, with a confirmed diagnosis of ADHD combined presentation by a specialist (psychiatrist, paidopsychiatrist, or a neuropsychologist), and without pharmacological treatment for ADHD in the last six months. The exclusion criteria were: a clinical history of seizures or electroencephalogram (EEG) with paroxysmal activity, or presence of a psychiatric history (except for Oppositional Defiant Disorder and Anxiety Disorder).

Psychological and Psychiatrist Tests

Two clinimetric tests were applied, the “Cuestionario para Escolares Y Adolescentes Latinoamericanos con Trastorno por Déficit de Atención Hiperactividad” (CEAL-ADHD from now on only CEAL) *[37]*, according to the DMS-IV-TR and standardized for the Mexican population *[38]*, and the DU-PAUL clinical test *[39]*. Both tests provide a total score and evaluate the main ADHD symptoms, except for tempo cognitivo lento (TCL), which is only evaluated by the CEAL test. These tests were applied before starting the rTMS protocol (basal stage) and after the 5th, 10th, and 15th (final stage) rTMS sessions. Also, a MINI-KID Child and Adolescent Psychiatric Interview *[40]* and a SHIPLEY-2 IQ Test *[41]* were conducted. Furthermore, an EEG was performed to confirm the absence of epileptiform activity.

Experimental Design

EMTr application

For this study, a high-performance TMS magnetic stimulator MaqPro R30 (MagVenture, Denmark) and a Cool D-B80 butterfly coil (120º angle) (MagVenture, Denmark) were used. In all the groups, the coil positioning was used according to the international 10-20 system. On the other hand, to determine both the site of motor cortex stimulation (motor threshold searching), and the area proposed by this protocol (middle line) for active stimulation (Fpz) *(Figure 1A)*. Two phases were considered for this study: the first phase was performed with two groups (each one with n=9) and according to the protocol criteria mentioned above. The first group (ACTIVE) received a high-frequency rTMS treatment of 5 Hz rTMS, with a total of 1500 pulses (30 trains of 50 pulses per train, with inter-train intervals of 10s), and over the m-PFC at 100% of their motor threshold during 15 sessions (Figure 1B). The second group (SHAM) corresponds to individuals who, in their first 15 sessions did not receive active stimulation (the magnetic field

was not in contact with the scalp of the patient since the coil was positioned vertically), but the generated sound by the coil remained *(Figure 1C)*, and subsequently, this group received 15 active sessions.

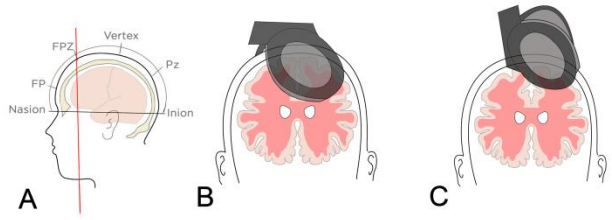

Figure 1: Scheme of the positioning of the double angled coil. A) According to the international 10-20 system, both coils were positioned over the Fpz Area (Red line), B) Position used for the ACTIVE group C) Position used for the SHAM group.

In the second phase, the individuals from the ACTIVE and the SHAM groups with severe ADHD clinical symptoms according to the clinimetric tests (CEAL-ADHD and DU-PAUL) were included as two separate groups (each group with a n=5). Additionally, two groups (each one with a n=5) were included in this phase; the (5 Hz+MTP) group, which received a high-frequency rTMS treatment with MTP, and finally, the (1 Hz + MTP) group, which received a low-frequency rTMS treatment with MTP *(Figure 2).*

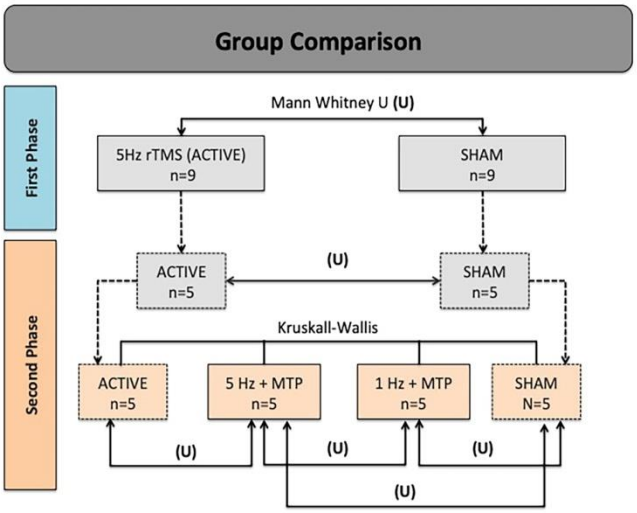

Figure 2: Study process diagram. The two phases were carried out in this study; the first phase (blue) and the second phase (orange). The ACTIVE and the SHAM groups were compared using a Mann-Whitney U test; subsequently two groups derived from the ACTIVE group and the SHAM group were included in the second phase, these were compared by Mann-Whitney U test (U) and finally a comparison among the ACTIVE, the 5 hz+MTF, 1 Hz+MTP and SHAM groups was carried out. Solid lines indicate the statistical analysis performed, and dotted lines indicate the process that the ACTIVE group and the SHAM group follow in the study.

Data Analysis

For the comparison of the basal and final stage scores from the CEAL and DU-PAUL tests, were carried out by non-parametric statistical tests *(Figure 2).* In the first phase, the ACTIVE group (n=9) was compared against the SHAM group (n=9) using the Mann-Whitney U test. In the second phase, the ACTIVE groups with severe symptoms and the SHAM group with severe symptoms were compared against the 5 Hz+MTP and 1 Hz+MTP groups using a Kruskal-Wallis test. A Mann-Whitney U test was subsequently performed to compare: The ACTIVE group of the second phase vs. the 5 Hz+MTP; the group 1 Hz+MTP vs. 5 Hz+MTP; the SHAM group vs. 5Hz+MTP, and the SHAM group vs. the 1Hz+MTP *(Figure 2).* Also, a percentage change analysis was carried out to determine clinical improvement. Data analysis was carried out with SPSS v 21.0 software.

Statement of ethics

This study was carried out with the approval of the "Comité de Bioética del Instituto de Neurobiología de la Universidad Nacional Autónoma de México, UNAM" (Research protocol INB 45-H). The patients always attended the tests in the company of their parents/guardians, who signed the letter of informed consent.

Results

Thirty individuals were initially included in the study. Subsequently, two individuals were discarded from the study for reporting marijuana use. The final sample was 28 Mexican male adolescents, with an average age of 14.6±1.6 years old and a combined ADHD diagnosis. Regarding the first phase analysis, no significant differences were found between the ACTIVE group and the SHAM group at the basal stage evaluation [CEAL-ADHD, U=39,p=0.93; DU-PAUL, U=33.50, p=0.66], and at the final stage evaluation CEAL-ADHD (u=28.50, p=0.29); DU-PAUL (U= 27.50, 0.25). On the other hand, a Kluskal-Wallis test using to analyze the second phase at the basal stage for the four groups evaluated did not show significant differences among them [CEAL-ADHD, p=0.897; DU-PAUL, p=0.312], neither the final stage [CEAL-ADHD, p=0.206; DU-PAIL, p=0.075]. Further analysis using Mann-Whitney U test at the basal and final stages for all the groups evidenced that the groups 1Hz+MTP and 5Hz+MTP showed significant differences when comparing versus SHAM. Also, the ACTIVE group showed significant differences compare with the SHAM group *(Tables 1 and 2)*

CEAL- ADHD

		1st PHASE			2nd PHASE													
		ACTIVE vs SHAM			ACTIVE vs SHAM			ACTIVE/5Hz+MTP			SHAM/1Hz+MTP			SHAM/5Hz+MTP			1Hz+MTP/5Hz+MTP		
		n=9 / n=9			n=5 / n=5			n=5 / n=5			n=5 / n=5			n=5 / n=5			n=5 / n=5		
	Ss	Mdn	U	p	Mdn	U	p	Mdn	U	p	Mdn	U	p	Mdn	U	p	Mdn	U	p
TOTAL	Bss	51/55	39.0	0.93	61/64	11.0	0.84	61/55	5.0	0.15	64/55	10.0	0.69	64/55	4.50	0.09	55/55	12.00	1.00
	15ss	31/37	35.0	0.66	32/48	3.5	**0.05**	32/26	7.0	0.31	48/28	0.00	**0.008**	48/26	0.00	**0.008**	28/26	11.00	0.84
INAT	Bss	28/32	33.5	0.54	32/36	7.0	0.31	32/28	5.0	0.15	36/33	5.50	0.15	36/28	0.00	0.008	33/28	3.00	**0.05**
	15ss	16/23	32.5	0.48	21/31	4.0	0.09	21/13	7.5	0.31	31/15	0.50	0.008	31/13	1.50	0.01	15/33	11.50	0.84
HIP/IMP	Bss	19/15	25.5	0.19	25/18	5.5	0.15	25/23	7.5	0.31	18/22	12.50	1.00	18/23	10.50	0.69	22/23	11.00	0.84
	15ss	8/11	37.0	0.79	12/13	8.5	0.42	12/11	11.0	0.84	13/9	5.50	0.15	13/11	5.50	0.15	9/11	11.00	0.84
T.C.L	Bss	7/7	38.0	0.86	7/9	10.0	0.69	7/8	11.5	0.84	9/8	7.50	0.31	9/8	9.50	0.54	8/8	10.50	0.69
	15ss	4/5	29.5	0.34	5/8	2.0	0.03	5/3	6.5	0.22	8/4	0.00	0.008	8/3	0.50	0.008	4/3	11.00	0.84

Table 1: Statistical significance observed, in CEAL scale, when comparing the median of the basal and total scores, between the groups in phase 1 and 2.

DU-PAUL

		1st PHASE			2nd PHASE														
		ACTIVE / SHAM			ACTIVE / SHAM			ACTIVE / 5Hz+MTP			SHAM/1Hz+MTP			SHAM/5Hz+MTP			1Hz+MTP/5Hz+MTP		
		n=9 / n=9			n=5 / n=5			n=5 / n=5			n=5 / n=5			n=5 / n=5			n=5 / n=5		
	SESSION	Mdn	U	P	Mdn	U	p	Mdn	U	p	Mdn	U	p	Mdn	U	p	Mdn	U	p
TOTAL	Bss	33/39	28.5	0.29	44/42	11.0	0.84	44/38	8.0	0.42	42/31	8.50	0 .42	42/38	5.00	0.15	31/38	10.50	0.69
	15ss	15/27	27.5	0.25	22/30	2.0	**0.03**	22/15	7.0	0.31	30/14	0.00	**0.008**	30/15	0.00	**0.008**	14/15	10.00	0.69
INAT	Bss	20/24	23.0	0.13	21/24	6.0	0.22	21/20	7.0	0.42	24/21	4.00	0.09	24/20	1.50	0.01	21/20	10.00	0.69
	15ss	9/14	23.0	0.13	11/19	2.0	**0.03**	11/8	7.5	0.31	19/8	0.00	**0.008**	19/8	0.50	0.008	8/8	12.00	1.00
HIP/IMP	Bss	14/16	38.5	0.86	23/16	8.5	0.42	23/18	9.0	0.54	16/13	11.00	0.84	16/18	9.00	0.54	13/18	10.00	0.54
	15ss	4/5	35.0	0.66	11/13	8.0	0.42	11/6	9.0	0.54	13/6	1.50	**0.01**	13/6	1.50	**0.01**	6/6	11.00	0.84

Table 2: Statistical significance observed, in DU-PAUL scale, when comparing the median of the basal and total scores, between the groups in phase 1 and 2.

Concerning the percentage change, the present study showed that, at the end of the treatments, SHAM group showed percentages of change of less than 35%, compared to the active groups that had significant clinical improvement *(Table 3, Figure 3).*

PERCENTAGE CHANGE				
	GROUP	Bss/5ss	Bss/10ss	Bss/15ss
CEAL-ADHD	1 Hz + MTP	18%	36%	49%
	5 Hz + MTP	37%	47%	49%
	SHAM	17%	0.0%	25%
	ACTIVE	16%	21%	48%
DU-PAUL	1 Hz + MTP	35%	52%	61%
	5 Hz + MTP	52%	46%	59%
	SHAM	10%	19%	28%
	ACTIVE	16%	39%	50%

Table 3: Percentages of observed changes, between the baseline scores, in both scales and those registered after 5ss, 10ss, 15ss, respectively, in the four groups evaluated.

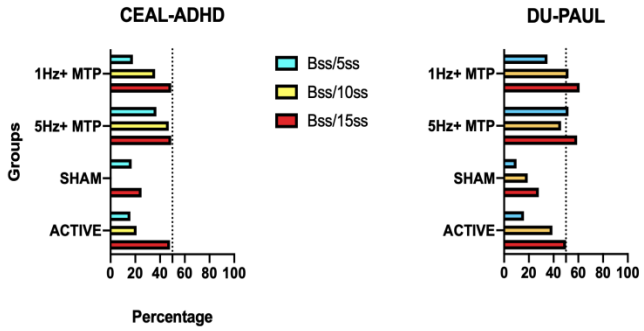

Figure 3: Percentages (axis X) for all groups (axis Y), in different moments of the protocol. Basal (Bss), 5th session (5ss), 10th session (10ss). The dotted line represents the cut-off point at which a treatment is considered effective (50%).

Conclusion

Up today, all rTMS protocols in the pediatric population have involved the DLPFC, right or left, and high or low-frequency rTMS (≥5Hz or ≤1Hz) [15-21]. Considering that OCD has clinical and neurobiological links with ADHD and stimulating results have been obtained with deep transcranial magnetic stimulation, the use of a DCC on dmPFC could be an option for the treatment of ADHD. Our research group has used, for more than a decade, the 5Hz rTMS on the DLPFC with MDM, OCD and Borderline Personality Disorder, with clinical improvement in its symptoms *[42]*. Our experience, in terms of frequency, coincides with that of Phillip et al. [43], who concluded that the stimulation at 10 Hz (more annoying) on the left CPDL was similar to that of 5 Hz (more tolerable). This work was divided into two phases. In the first one, we obtained that both ACTIVE and SHAM groups of patients do not improved with rTMS (5 Hz) on the dmPFC. Weaver *[22]* reported similar results but using 10 Hz in the right DLPFC of a group of adolescents (14-21 years). The two groups of patients (ACTIVE and SHAM) were chosen randomly with n=9, and no significant differences were found between their baseline scores in both clinical scales. Considering the severity of symptoms groups were reduced to n=5 in both, and then significant differences were obtained in the pre-post rTMS, only in the active group. This favorable effect of rTMS to reduce ADHD symptoms coincides with that reported by Gómez et al. *[23]*, Mekki et al. *[24]*, and Cao et al. *[25]* in children between 6-13 years of age, although using different stimulation protocols. Mekki et al. (24) evidenced the benefit of rTMS, at 1 Hz, on the severity of ADHD symptoms, while Cao et al. *[25]* highlighted the importance of associating the rTMS, at 10 Hz, on the DLPFCwith treatment with Atomoxetine. In the second phase of this research, the two groups under medical treatment (MTP) were included, both with n=5. It was observed that the 3 ACTIVE groups (rTMS at 5 Hz, alone or with MTP, and rTMS at 1 Hz) and the SHAM group, did not show significant differences in the basal scores of both clinimetric scales. However, at the end of each rTMS protocol over dmCPF, there were significant differences ($p \leq 0.01$) between the four groups in the scores of the clinical scales. The inter-group contrasts evidenced significant differences between the ACTIVE groups and the SHAM, especially in the group treated with MTP *(Tables 1 and 2)*. In addition to the clinical improvement evidenced by the statistical analysis for small samples, another approach to evaluate the benefit on the symptomatology of adolescents was the analysis of the percentages of change *(Table 3)*. Some authors *[44]* consider that a decrease in the 50% or more of the score, on clinimetric scales, represents a favorable clinical response. In our research, it was found that at the end of the treatments, the SHAM group showed percentages of pre-post rTMS change below 30%; while in the ACTIVE groups the percentages were very close to or exceeded 50%, especially on the DUPAUL scale and for the groups treated with MTP. It is important to note that some factors may modify the effectiveness of the rTMS. Among them, some are related to the coil or the protocol itself, while others depend on the patient *[28,45]*. For example, the inter-train interval may be crucial yielding the rTMS-induced neuroplasticity *[46]*; that is, "inhibitory" response with rTMS at 5 Hz, instead of excitatory, but of lower power than that achieved with 1 Hz. Considering these factors may contribute to decreasing the inter-individual variability that can affect so many group reports.

Finally, adolescence constitutes a window of opportunity to carry out different treatments *[1]*, especially in those childhood illnesses that continue until this stage, as it can happen in ADHD. Although this research had an exploratory purpose, and the sample was small to reach definitive conclusions, promising preliminary results were obtained. When the severity of the symptoms was taken into account, it was found that there

was a significant clinical improvement in the groups with active stimulation compared to the SHAM group; especially in adolescents who had not improved their symptomatology using only the MTP in the six months before rTMS. Therefore, it is suggested to replicate this methodology in a larger sample, controlling the benefits of this type of treatment by applying, before and after it, neuropsychological tasks and/or taking into account electrophysiological variables that provide direct information about the subject and contribute to the neurobiological interpretation of the changes that respond to clinical improvement. In summary, to the best of our knowledge, this study is the first to explore the effects of rTMS at 5 Hz, using a double cone coil and stimulation of dmCPF in adolescents with ADHD, drug-free and MTP treatment.

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Conflict of Interest

The authors have no conflicto of interest to declare.

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