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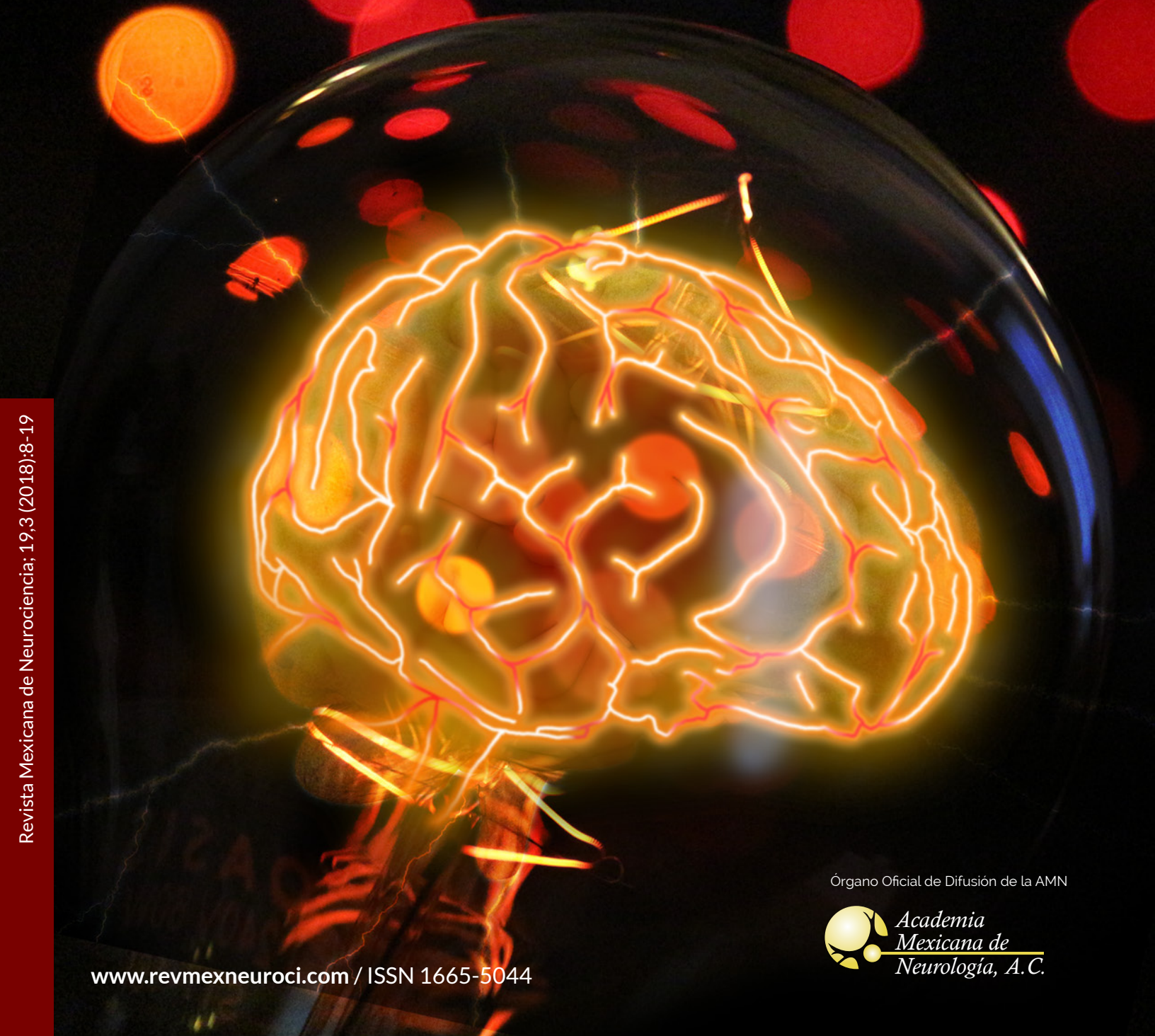

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# Original contribution

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## Safety and effectiveness of non-invasive brain stimulation in autism spectrum disorder: results of a proof-of-concept study

Seguridad y efectividad de la estimulación cerebral no invasiva en el trastorno del espectro del autismo: resultados de un estudio de prueba de concepto

## Abstract

**Introduction.** Autism Spectrum Disorder(ASD) still being a therapeutic challenge for neurosciences. Different pharmachological and non-pharmachological treatments have been developed inducing benefits in ASD patients in some degree, with cumulative effect; but more research is needed to improve clinical results. There are evidences about the potential positive effects of Non-Invasive Brain Stimulation(NIBS) in ASD patients.

**Objective.** To evaluate the safety and effectiveness of NIBS in patients with ASD.

**Methods.** We carried out a proof of concept study including 15 children with ASD according to DSM-5 diagnostic criteria. They proceeded from the ambulatory services of the International Center for Neurological Restoration and Borrás-Marfán Hospital(Havana, Cuba). Inclusion criteria established that children should had no change in their therapeutic approach one month before the intervention; and an equivalent period of stabilization of their symptoms. Repetitive Transcranial Magnetic Stimulation(rTMS) and Transcranial Direct Current Stimulation(tDCS) were used as stimulation methods; tDCS(cathode F3, anode right arm) was used in children under 10 years and 11 month; and 1 Hz rTMS for children over 11 years. Stimulation was focalized over the left dorsolateral prefrontal cortex, and a total of 20 session were applied. Patients were evaluated before and one week after the intervention applying the Autism Treatment Evaluation Checklist(ATEC), the Autism Diagnostic Interview(ADI-R) and the Autism Behavior Checklist(ABC).

**Results.** Only in one patient it was not possible to start the treatment because of poor collaboration. The other 14 completed

the 20 sessions with a few adverse effects, basically local pain at the stimulation site. A significant change in clinical scales was observed, with lower scores in the second evaluation, (ADI-R: initial= 52±9, final=44.4±7; ATEC: 58±19.4 and 41±14.7; ABC: 108.4±23.7 and 89±17; $p<0.05$); indicating a clinical improvement in the group of patients.

**Conclusions.** NIBS was well tolerated and induced behavioral changes in our sample of patients in key aspects of autistic behavior.

## Keywords

*NIBS, rTMS, tDCS, Autism Spectrum Disorder.*

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# Resumen

**Introducción.** El Trastorno del Espectro del Autismo(TEA) es un desafío terapéutico para las neurociencias. Se han desarrollado diversas intervenciones farmacológicas y no farmacológicas con resultados beneficiosos; pero se requieren de más investigaciones para lograr mejores resultados clínicos. Existen evidencias sobre los beneficios potenciales de la Estimulación Cerebral No Invasiva(ECNI) en estos pacientes.

**Objetivo.** Evaluar la seguridad y la efectividad del uso de la ECNI en niños con TEA.

**Métodos.** Se realizó un estudio de prueba de concepto que incluyó 15 pacientes con diagnóstico de TEA según criterios del DSM-5, procedentes del Centro Internacional de Restauración Neurológica y del Hospital Pediátrico Borrás-Marfán(Habana, Cuba). Como criterio de inclusión se definió la no modificación del esquema terapéutico de los pacientes, y la existencia de estabilidad clínica 1 mes previo a la intervención. Se utilizaron dos métodos de ECNI: la estimulación magnética transcraneal repetitiva(rTMS) y la estimulación transcraneal con corriente directa(tDCS). Los pacientes hasta 10 años y 11 meses recibieron tDCS(cátodo F3; ánodo brazo derecho); a partir de 11 años de edad la rTMS(1 Hz). La estimulación se focalizó sobre la corteza prefrontal dorsolateral del hemisferio izquierdo, con un total de 20 sesiones. Los pacientes fueron evaluados antes y una semana después de la intervención mediante la Escala de Evaluación de la Respuesta Terapéutica en el Autismo(ATEC), la Entrevista Diagnóstica para el Autismo(ADI-R) y la Lista de la Conducta Autista(ABC).

**Resultados.** En un paciente no fue posible iniciar el tratamiento por poca colaboración. Los restantes 14 completaron la intervención con pocos efectos adversos, básicamente molestias locales en el sitio estimulado. Se observó una disminución significativa en la puntuación de las escalas clínicas en la segunda evaluación (ADI-R: inicial= 52±9, final=44.4±7; ATEC:58±19.4 y 41±14.7; ABC:108.4±23.7 y 89±17; $p<0.05$); indicando una mejoría clínica grupal.

**Conclusiones.** La ECNI fue bien tolerada e indujo cambios conductuales en la muestra de pacientes en aspectos claves de la conducta autista.

**Palabras clave**

*ECNI, rTMS, tDCS, Trastorno del Espectro del Autismo.*

# Introduction

Autism Spectrum Disorder (ASD), according to the current criteria defined in the DSM-5, includes a spectrum of manifestations characterized by severe deficits and generalized alterations in multiple areas of development. In these patients, there are alterations in social interaction, communication disorders, and the presence of restricted and stereotyped behaviors, interests, and activities. The term ASD currently encompasses four different diagnoses that existed in the previous DSM-IV classification but, in essence, it is a clinical picture whose diagnosis, in most cases, involves a high degree of disability.[1] The figures for ASD prevalence fluctuate between different countries. In the USA, the prevalence in children aged up to 8 years old is 1 in 68;[2] in France, it's 0.36 per 100 children;[3] and in Mexico, there is 1 case for every 115 children.[4] In general, reliable epidemiological data regarding this disorder can be scarce in developing countries.

Recent advances in neuroscience have allowed us to know more about the pathophysiology of ASD, especially in terms of brain connectivity patterns that are far from what has been described in normal subjects.[5] As in other diseases, unfortunately, there are no great advances in therapeutic approaches; although it is noteworthy that the use of various methods of fundamentally non-pharmacological treatments can be favorable in terms of controlling autistic symptoms, facilitating a better integration of the patient with their family and social environment.[6] From the pharmacological point of view, there is still no single, specific drug for the treatment of ASD. The use of risperidone, aripiprazole, carbamazepine, valproic acid, and methylphenidate, among others, stand out internationally according to the prevailing symptoms and comorbidity with other pathologies.[7,8] All the therapies described in the literature benefit patients with ASD and, although traditional or alternative medicine can be added, it is agreed by consensus that more scientific research is needed to define better therapeutic strategies that would allow achieving superior clinical results.[9]
Bailey et al. were among the first to point to the cerebral cortex as key in the pathophysiology of ASD.[10] Casanova et al. subsequently drew attention in a series of investigations to the existence of anomalies in the minicolumnar organization of the cerebral cortex, including the existence of smaller neurons increased in number and density per unit area, periventricular heterotopias, and cortical dysplasia, in addition to a significant reduction of the neuropil, which results in an inhibitory intracortical dysfunction, an aspect that possibly contributes significantly to much of the autistic symptomatology.[11,12]

A large amount of research has been developed in recent years using non-invasive brain stimulation (NIBS) methods such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). These methods, depending on the specific protocol used, may have an effect that enhances cortical inhibition or an increase of excitability in the circuits to which they're applied.[13,14] Both rTMS and tDCS are methods that are widely used currently for the symptomatic control of various diseases with differences in the levels of scientific evidence. Major depression, chronic pain, post-traumatic stress, and fibromyalgia account for the highest levels of scientific evidence right now.[15,16]

Several articles have been published that provide evidence for the favorable effect that these methods can have on the control of autistic behavior even with changes in the expression of some electrophysiological responses, although mostly with the application of a low number of sessions to expect a significant and lasting clinical effect. In other diseases, where the clinical effect of these interventions is better known (e.g. depression), the use of at least 20 sessions is recommended to ensure greater efficacy.[17-19] On the other hand, there are no data to differentiate the efficacy of rTMS and tDCS as neuromodulators, an aspect that is of great importance as a guide for the selection of one over another method for therapeutic use.

In this article, we start from the hypothesis that

the use of NIBS can have an adjuvant effect in the treatment of children with ASD, and we set as the main objective to demonstrate the safety of the use of rTMS and tDCS in this particular disorder, as well as to obtain proof-of-concept type of evidence on the effect of both methods for the better control of the clinical symptomatology.

# Methods

Fifteen children diagnosed with ASD (13 males and 2 females, aged between 5 and 13 years), were included in this study. They were classified as moderate or mild according to the DSM-5 criteria and coincidental diagnostic impressions from the specialist in pediatric neurology and child and adolescent psychiatry. The patients came from the ambulatory care services of the Pediatric Teaching Hospital Borrás-Marfán and from the International Neurological Restoration Center, treated during the period of November 2015 to October 2016.

The criteria of inclusion included an agreement in diagnostic impression by the specialist in pediatric neurology and child and adolescent psychiatry, the maintenance of the same therapeutic scheme (pharmacological and psychopedagogical) during the month prior to starting the intervention, and stability of the symptomatology during that time. The clinical diagnosis was confirmed by applying the Childhood Autism Rating Scale (CARS)[20] and the Autism Diagnostic Interview (diagnostic algorithm), Revised (ADI-R).[21]

Any patients in whom comorbidity with epilepsy existed were excluded from the initial selection, as well as any who had modifications in their pharmacotherapy (in dose or type of medication) in the month prior to the recruitment for this investigation. In no case was the basic therapeutic scheme interrupted for any patient, only the appropriate stimulation protocol was added according to their age.

## Experimental design

Patients were recruited through continuous inclusion, as they visited their corresponding care services. The characteristics of the study were explained to the parents and the children were assigned a treatment group according to their age: 5 to 10 year-olds to the tDCS group, and 11 year-olds and older to the rTMS group. This differentiation was established because children older than 11 years of age generally collaborate better with the different evaluative procedures and more demanding technical requirements involved in the application of the rTMS. The tDCS was applied with a Neuroconn (GE) device, and the cathode was placed in the F3 position (10/20 system) as a projection guide for the left dorsolateral prefrontal cortex and the anode on the upper third of the right arm. Each session lasted 20 minutes and the stimulation had 1 mA of intensity. In each session of the other group, each patient received a total of 1500 pulses of 1 Hz rTMS at 90% of the motor threshold value (MagStim, UK), placing the center of the figure 8 coil on the same position. The patients sat comfortably during the stimulation sessions. They were shown cartoons of their choice on a television screen and, in some cases, they were also allowed to manipulate didactic toys and tablets with entertainment games to facilitate their cooperation. Every patient received 20 treatment sessions in total.

The patients were evaluated twice before starting the intervention. The ADI-R (algorithm for current condition),[21] the Autism Behavior Checklist (ABC),22 and the Autism Treatment Evaluation Checklist (ATEC)[23] were applied. These evaluations were performed again one week after completing the 20 treatment sessions. The evaluators did not directly participate in the application of the stimulation sessions in any of the cases.

Additionally, an electroencephalogram (EEG) was performed in the awake state before starting the treatment and one week after the end of the treatment, in order to corroborate whether changes in brain connectivity patterns were identified. An assembly of 19 active Ag-Cl electrodes was used on the scalp (Fp1, Fp2, F7, F8, F3, F4, C3, C4, T5, T6, T3, T4, P3, P4, O1, O2, Fz, Cz, Pz), according to the international 10/20

system, with references at the level of Cz and Pz. The impedance was kept below 5 k Ohm. For this analysis, 38 windows were selected free of artifacts from the electroencephalographic records in the awake state with open eyes in each patient's registry. The functional connectivity was analyzed from the calculation of the spatial synchronization matrix (synchronization likelihood) between the electrodes.[24,25] The following was determined for the five frequency bands: Alfa (8-12.9 Hz), Beta (13-29.9 Hz), Theta (4-7.9 Hz), Delta (1-3.9 Hz) and Gamma (only within the 30-35 Hz range). All the processing was performed using algorithms implemented on the MATLAB R2008b program, and the data matrices registered for each patient were compared before the intervention and after the intervention.

### Adverse effects

The children were closely observed during the stimulation sessions, looking for signs indicating local discomfort or any manifestation of abnormal cortical hyperexcitability induced by the intervention. The parents were questioned a day later about any behavioral changes they noticed in the child, especially in the first hours after the sessions ended.

### Medical ethics

The protocol was approved by the Scientific Council and the Institutional Ethics Committee of the International Center of Neurological Restoration. The informed consent was given in writing by the parents, who received an extensive oral and written explanation of the characteristics of the procedures. The ethical guidelines for human research included in the Code of Ethics of the World Medical Association (Declaration of Helsinki) were complied with for research involving humans.[26]

### Statistical Analysis

A nonparametric statistical analysis was performed using the Wilcoxon series test to compare the behavior of the scales in the two evaluative moments and the Mann-Whitney U to define if there were differences in the therapeutic response between groups with different interventions. Both cases considered an $\alpha=0.05$ (Statistica 7.0, Stat Soft Inc. 2004). Connectivity analysis based on the EEG also considered an $\alpha=0.05$ for the comparisons between the matrices of data extracted from the two evaluative moments, with the use of a Student's t-test.

## Results

### Tolerance and adverse effects

The final distribution of the sample according to the treatment method included a total of 9 children younger than 11 years old who received tDCS and 6 children older than 11 years who received rTMS; only 2 of them were female. The majority of patients showed good tolerance with both procedures, and only in an 8-year-old child (tDCS) therapy was not achieved due to lack of collaboration after several attempts to place the electrodes for stimulation on non-consecutive days. In the remaining patients it was possible to begin the treatment on the day it was proposed to start and complete it without interruption. The most frequent adverse effect reported or detected from the behavior of the children was the existence of local discomfort at the stimulation site (≈50%), which in all cases was slight and did not require any intervention, pharmacological or otherwise (Table 1).

Somnolence occupied the second place, which, according to the description of the parents, was expressed as the child sleeping one or two hours earlier than usual at night, with a quieter and more regular sleep, although this was not an aspect that was evaluated in depth.

### Effects of the intervention

In all the cases individually, the parents identified behavioral changes they spontaneously described qualitatively, which were also transmitted indirectly by teachers and other relatives, who were often unaware that the child was receiving an experimental intervention. Standing out among these changes were those related mainly to the improvement in socialization and communication;

additionally, there was a decrease in the variety and amount of stereotypies from the first week after the end of the intervention.

The initial and post-intervention evaluations were developed maintaining exactly the same conditions, variety of toys, and interactions. Evaluators similarly described qualitative and quantitative behavioral changes regarding the child's interactions during the interview, the characteristics of the game, and the degree of hyperactivity. These changes were reflected in the results of the statistical analysis of the scores of the clinical scales evaluated (Figure 1).

One week after completing the intervention there was a 15% reduction in the score of the scales compared to the initial score of the group. No differences were identified regarding the magnitude of the changes observed in the scales related to the method used (tDCS vs rTMS), even without considering the differences in average age between the groups (tDCS=8.7 years; rTMS=12.6 years), showing both methods to be effective as modulators of autistic behavior (Figure 2).

Modifications in brain connectivity based on the analysis of the α activity of the electroencephalogram.

The EEG-based connectivity analysis showed significant changes after the intervention, with an increase in functional connectivity at the alpha, beta, and gamma frequencies, especially in the latter ($p<0.05$). The same analysis for the slower frequencies (θ and δ) had an opposite behavior with a decrease in connectivity, especially in anterior regions ($p<0.05$). The topographic distribution of this increase in functional connectivity for the faster frequencies had a more diffuse character, including all regions, with a wider distribution in the case of the gamma (Figure 3).

Table 1. General characteristics and adverse effects observed in the sample studied.

| Patient | Age | Sex | NIBS | Comorbidity | Pharmacological treatment | Degree of severity | Completed the treatment | Local discomfort | Headache | Somnolence |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 5 | M | tDCS | - | CBZ | Mild | Yes | Yes | - | - |
| 2 | 5 | M | tDCS | - | CBZ, RPD | Mild | Yes | - | - | - |
| 3 | 8 | M | tDCS | - | CBZ | Moderate | No | - | - | - |
| 4 | 10 | M | tDCS | - | CBZ, RPD | Moderate | Yes | - | - | - |
| 5 | 13 | M | rTMS | - | - | Moderate | Yes | - | - | **Yes** |
| 6 | 13 | M | rTMS | - | CBZ, RPD | Moderate | Yes | - | - | - |
| 7 | 13 | M | rTMS | - | CBZ | Mild | Yes | - | - | **Yes** |
| 8 | 7 | F | tDCS | - | : | Mild | Yes | Yes | - | **Yes** |
| 9 | 13 | M | rTMS | - | CBZ | Moderate | Yes | - | Yes | **Yes** |
| 10 | 9 | M | tDCS | - | RPD | Mild | Yes | Yes | - | - |
| 11 | 10 | F | tDCS | - | CBZ | Mild | Yes | Yes | - | - |
| 12 | 8 | M | tDCS | - | - | Mild | Yes | Yes | - | - |
| 13 | 10 | M | tDCS | - | CBZ | Moderate | Yes | Yes | - | - |
| 14 | 7 | M | tDCS | ADHD | CBZ | Moderate | Yes | Yes | - | - |
| 15 | 11 | M | rTMS | - | CBZ | Mild | Yes | - | - | **Yes** |

Figure 1. Behavior of the scores on the clinical scales with the therapy (*p<0.05).

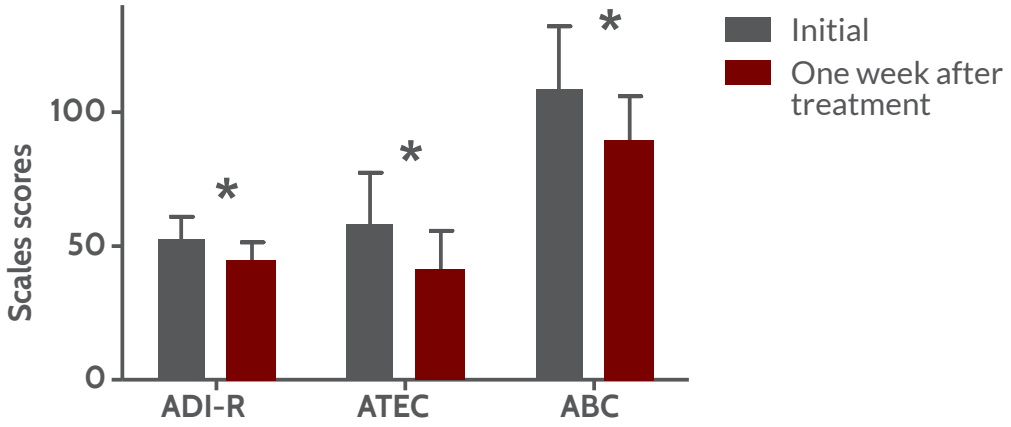



Figure 2. Differences between the scores of the clinical scales before and one week after completing treatment with tDCS and rTMS (p>0.05 in the three scales).

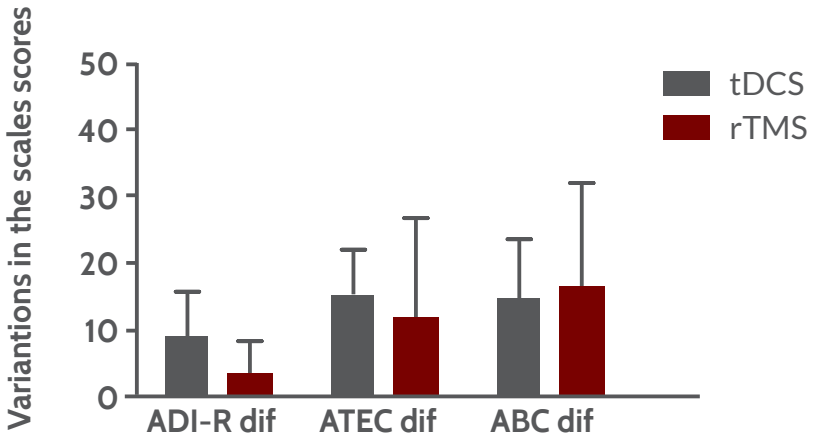
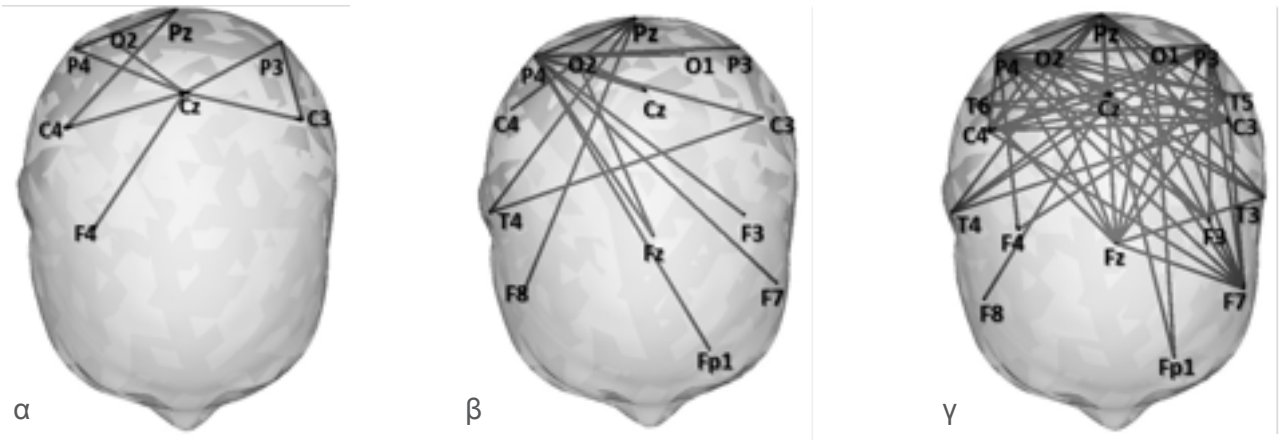



Figure 3. . Increase in functional connectivity between the points selected for the frequencies analyzed >8 Hz α, β and γ (only significant changes are represented, p <0.05).



# Discussion

The application of NIBS methods in the pediatric population has been limited in previous years due to the lack of data on their safety and potential adverse effects, to such an extent that the reference literature lists children under 18 years of age as a formal contraindication to the application of rTMS. The absence of evidence on their safety has not meant at any time that there is evidence that contraindicates its use in children under 18 years of age. Fortunately, it has only been a matter of time to demonstrate that the application of rTMS and tDCS is a safe, tolerable method and that it is associated with very few adverse effects, both in healthy subjects and in patients.[27,28]

The most frequent adverse effects described with these methods involve the presence of local discomfort, an observation we reported as one of the results of this work.[29,30] Secondly, the changes observed by the parents regarding sleep (reported as somnolence), are limited in all cases to the child going to bed earlier than usual and sleeping most of the night without interruptions--even the patients who typically slept little or had a very restless sleep with frequent awakenings. This description is interpreted as an improvement in the structure and quality of sleep, even though this had not been one of the preconceived objectives of this research. It was a beneficial side effect in all the cases in which it was reported and, though not widely reported in the literature, it is a known effect.[31] In no case did seizures or other phenomena of abnormal cortical hyperexcitability occur.

The most interesting result in this research was the significant improvement in autistic symptoms in all the children who received the intervention, achieving an additional reduction of 15% in the score of the clinical scales compared to just basic treatment. This coincided qualitatively with the overall clinical impression of the evaluators, the large majority of whom were also the specialists who had been following up with these patients since their initial diagnosis. As a prominent aspect, a very significant improvement in socialization was observed, although from the point of view of the clinical scales the effect was global; and in second place, all aspects of language improved. Unlike research published by other groups, our study used a much larger number of sessions than what has been used so far in patients with ASD,[32,33] and the clinical results seem very consistent when contrasting the results of the scales and the qualitative behavioral change in the patients.
No significant differences were identified in the modulatory effect between rTMS and tDCS in the expression of autistic symptomatology. The values for both groups moved in a similar range after treatment, even though the average age of the groups was different. Such an effect does not seem to be related to the age of the patients. This is an element that has not been addressed in the literature and can be an interesting starting point as it contrasts the use of a more expensive and technically demanding method (rTMS) with a cheaper, technically less demanding method, both yielding similar results, so that the cost-benefit ratio may be in favor of the extended use of tDCS. The rTMS is currently the NIBS method with the greater number of scientific evidence, so we just posit a hypothesis that requires more research to corroborate its veracity.[34-36] NIBS cannot currently be recommended as a valid therapeutic alternative for ASD due to lack of sufficient scientific evidence, but there are several indications that allow us to believe it could be in the near future. The heterogeneity in terms of methods is striking when analyzing the results of small published clinical trials with good apparent results and with the use of inverted stimulation polarities in the case of tDCS.[33,37]

The limitation of this study was the absence of a control group and/or placebo, which does not completely rule out the subjective factor in patients, family members, and evaluators, though we did start from an experimental design in which the concomitant use of other therapies was controlled, while also requiring the patient to have a period of at least one month of stability

both in their therapeutic scheme as well as in their symptomatology. Hence, the patients receiving the intervention were their own controls, so there is a high probability that the observed changes were secondary to the intervention and not to another cause. A sample increase and a design that includes a control group and the use of a placebo would be key to reach solid conclusions regarding the effect of these interventions.

Considering the elements that have been described about the pathophysiology of ASD,[12,38] which is based on an inhibitory intracortical dysfunction that motivates the alterations in the functional connectivity between brain areas, [39] the beneficial effect may be associated with the increase in functional connectivity between cortical areas dependent on the activity of the frequencies in the range of activity α, β and γ. Particularly with regard to this last band of frequency, this study only analyzed the lower component (30-35 Hz) in the waking state, at rest with eyes open. It is known that the spectral power of the γ activity is dependent on the functional state of the brain and that its increase is generally associated with the process of attention in normal subjects, showing a high degree of interhemispheric coherence. It seems that in patients with ASD, although most of the studies describe the increase in the spectral energy of this frequency band, it differs from normal records precisely in their degree of coherence. It has been described that the increase in connectivity of the γ band, especially in posterior regions, is associated with a higher level of functioning in ASD.[40] There seems to be a link between γ activity and ASD. In our case, the increase in functional connectivity dependent on gamma activity was associated with clinical improvement. There's not much more to say about it at the moment, but it is an aspect that deserves more attention, pending a definition of the type of relationship between this functional change and the therapeutic effect of NIBS.

# Conclusions

The use of Non-Invasive Brain Stimulation is tolerable in children with Autism Spectrum Disorder and induces significant changes in key aspects of autistic behavior, with increased functional connectivity between cortical areas depending primarily on the fastest frequencies.

## Conflicts of interest
The authors state that there are no relevant conflicts of interest in this study.

## Funding sources
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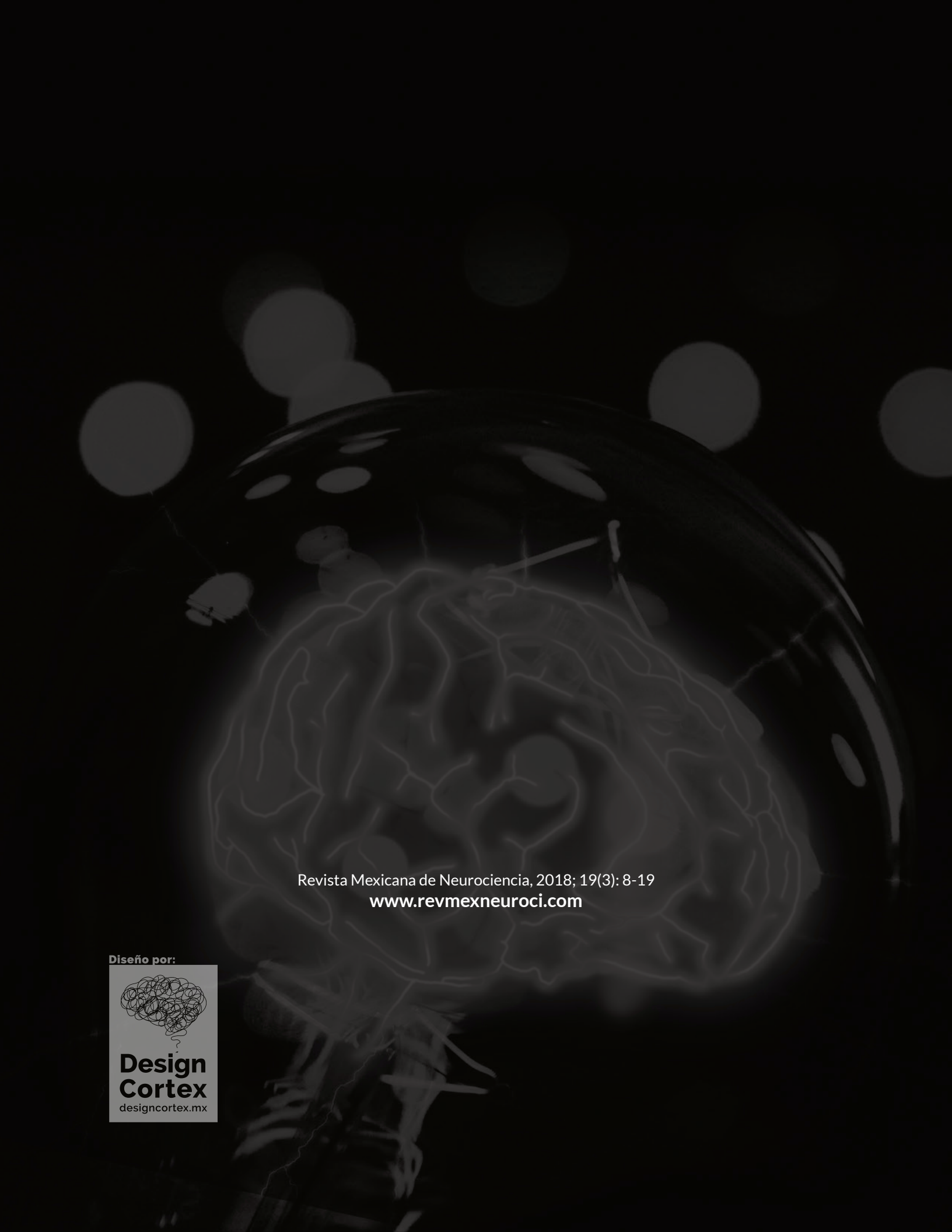

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