TITLE :

Efficacy and mechanistic of repeated transcranial magnetic stimulation in children with autism spectrum disorder: an open-label clinical trial

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PRINCIPAL INVESTIGATOR:

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Informed Consent Form

(Legal Guardian Edition)

Dear parents or legal guardians:

We would like to invite you and your child to participate in a study: Efficacy and mechanisms of repeated transcranial magnetic stimulation in children with autism spectrum disorders: an open-label clinical trial. Your child's participation in this study is completely voluntary. This informed consent form will provide you with important information about the study, so please read it carefully before deciding whether or not to participate in the study. If you have any questions or do not understand something, please ask the investigator for this research project and our team will answer all the questions you may have.

This study is sponsored by Fei Li, Chief Physician, and is being conducted by Dr.Li and her team at Xinhua Hospital, Shanghai Jiao Tong University School of Medicine.

1. What is the background and objectives of this study?

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation technology that alters the excitability of neurons and induced cortical functional reorganization by distributing rapidly changing magnetic fields through the magnetic coil tightly attached to the patient's scalp, and is currently been widely used in the study of neural mechanism and related treatments of neurological diseases. Previous studies have found that rTMS may be promise in helping patients with autism spectrum disorder (ASD) to alleviate their symptoms and is also relatively safe with mild and controllable side effects. However, to date, there have been few studies of rTMS targeting primary motor cortex (M1), and no studies have examined the effects of rTMS intervention on M1 in patients with ASD. Continuous theta pulse stimulation (cTBS) is a more efficient form of rTMS that produces stronger brain plasticity changes through lower overall stimulation intensity and shorter stimulation duration. Before the study plan, our team has included 20 cases of 6-10 years old high-function ASD children with a 10-day cTBS on left M1. They were followed up from baseline to 4 weeks after the end of the 10-day intervention in terms of clinical symptoms and adverse effects, and the results suggested that more than half of children had improvements in social and language function, meanwhile, it was safe and well tolerated.

This open-label clinical trial, we plans to recruit at least 30 cases of ASD children aged over 4 years old to undergo accelerated cTBS on left M1 for 5 consecutive days to explore the clinical efficacy of rTMS intervention, effective adaptation population, appropriate intervention mode and related neurophysiological mechanism.

2. What do you need to do before attending the study?

If you and your child decide to participate in this study, we will ask you to sign this informed consent form before conducting the study-related activities. If a new version of the informed consent form is generated during the study, you will need to sign it again.

3. What will happen if you and your child participate in the study?

It will take about 5 weeks for your child to complete this study.

After participation in the study, the following procedures will follow:

Screening visits

The study will begin with a screening visit after signing this informed consent form. The purpose of the screening visit is to find out if your child meets the requirements for participation in this study.

To be completed during the screening visit phase are: physical measurements, demographic data and history taking of your child by the physician, and your child need complete Intelligence tests, Autism Diagnostic Observation Scale (ADOS), Childhood Autism Rating Scale (CARS), Repetitive Behaviors Scale-Revised (RBS-R), Social Responsiveness Scale (SRS), Conners Parent Rating Scale (PSQ), Behavior Rating Inventory of Executive Function (BRIEF), Chinese Communication Development Scale (CCDI), Peabody Picture Vocabulary Test (PPVT) and language expression assessments. EEG signals will be captured when your child is watching cartoon video.

At the end of the screening visit, the study investigator will determine if your child is eligible to continue in the study. If your child cannot be able to participate in the study, the investigator will also explain why and discuss other treatment options with you.

Intervention process

Once your child has passed the screening process, the study physician will consult with you about the start of the intervention. At the start of the intervention, a trained and approved technician will assist your child to put on a cloth positioning cap and set the stimulation target (left primary motor cortex, M1). According to the international standard parameters, each stimulus session for 120s, 10 sessions a day (with a 50-60 min break) for 5 consecutive days.

Follow-up visit

After 5-day intervention, your child will complete clinical assessments within 3 days after the completion of the cTBS course (post-intervention) and 4 weeks after the last cTBS session (4-week follow-up), respectively.

Post-intervention and 4-week follow-up assessments:

Complete the Social Response Questionnaire (SRS), Repetitive Behaviors Scale-Revised (RBS-R), Conners Parent Rating Scale (PSQ), Behavior Rating Inventory of Executive Function (BRIEF) and Clinical Global Impression Scale (CGI) . EEG signals will be captured when your child is watching cartoon video.

Only 4-week follow-up assessments:

Complete the Social Responsiveness Scale (SRS), Childhood Autism Rating Scale (CARS), Repetitive Behaviors Scale-Revised (RBS-R), Conners Parent Rating Scale (PSQ), Behavior Rating Inventory of Executive Function (BRIEF), Clinical Global Impression Scale (CGI), Chinese Communication Development Scale (CCDI), Peabody Picture Vocabulary Test (PPVT) and language expression assessments. EEG signals will be captured when your child is watching cartoon video.

4. What are the possible risks and discomforts present in this study? Are there any corresponding protection measures?

The assessments during the trial may cause psychological fear, loneliness away from the family, and other psychological discomfort in your child. In addition, the questions asked by the doctor may make you and your child feel tired or embarrassed.

The intervention technicians were professionally trained and passed the examination. While receiving the experimental intervention modality, your child may experience physical and psychological discomfort including scalp discomfort, localized pain, dizziness, headache, fatigue, tinnitus, anxiety, etc. Most of these discomforts will resolve within 24 hours, while serious side effects of seizures and neurocardiogenic syncope have been reported to be induced during previous studies, but subjects who experience these two adverse reactions have a history of depression and/or syncope. The study is being to conduct in a hospital setting, and your child will be closely monitored and supported in case of adverse reactions, and a pediatrician will be available to provide treatment and follow-up if medical treatment is needed. In addition, your child will continue to be followed up for 4 weeks after the end of the intervention and will be given timely and appropriate treatment.

5. Are there other treatment options available besides participation in this study?

In addition to participating in this study, the treatment options for ASD children are: other behavioral intervention e.g., Applied Behaviour Analysis (ABA).

6. What are the possible benefits of participating in this study?

The intervention programs in this study may cure the disease or slow its progression. However, participation in this study also may not result in an improvement in your child's symptoms. Your child may not directly benefit, but information about the study will help to gain important information about ASD, and your participation may give hope to future patients suffering from the same condition.

7. What might you face if your child was harmed as a result of participating in this study?

During the course of the study, if your child experiences any discomfort or adverse event, whether or not related to the study or device, please inform your child's study physician, and your child will receive timely appropriate management and treatment.

Even if you have signed this informed consent form, you retain all of your legal rights.

8. Is this study a mandatory?

No, participation in this study is entirely voluntary. You may refuse to allow your child to participate, or you may withdraw from the study at any time during the study. Withdrawal from the study will not result in fines, discrimination or retaliation, and will not affect your child's future treatment or rights.

If you want your child to withdraw from the study, you should let us know timely. We will ensure that he/she is able to end the study in the safest way possible.

The decision to withdraw your child from the study can be made by the study investigator without your consent if one of the following occurs:

- You or your child did not follow the guidance of the research team;
- The study investigator believed that the study will not provide the maximum benefit to your child;
- The study was stopped by the study sponsor, the Ethics Committee (the organization that reviews the study to protect your rights), or a regulatory authority;

9. What should your children and you do after participating in the study?

After participating in the clinical study, you and your child need to follow the instructions of the researchers during trail:

- You and your child should try to cooperate with the researchers by completing each visit and all related assessments on time;
- Completing the diary cards on time and following the researcher's instructions to bring them back to the research center on time;

- If your child needs any other treatment due to changes in his/her condition, you need to consult the study physicians in advance or tell them promptly afterwards.

10. What happens if any new information comes up?

During the study, you will be contacted promptly about any meaningful new developments or new medical information related to your child's health.

Based on this new information, your study physician may also recommend that you withdraw from the study. The study doctor will explain why and discuss with you how better to treat your child.

11. If your child participates in this study, what fees will you pay?

Your child's participation in the study is free of charge for the intervention and related examinations such as behavioral assessments, scale evaluations and cognitive psychological tests.

12. Will you receive a grant for participating in this study?

You and your child will not receive any subsidies for participating in this study.

13. If your child participates in this study, how will his / her privacy be protected?

We will make every effort to protect the privacy of you and your child to the extent permitted by law. Any public reporting of the results of this study will not disclose any personal information about you or your child. Case information from this study may be accessed by the investigator, the Medical Ethics Committee of Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Dr. Li, or government agencies overseeing the process of this study.

All of your child related documents will be distinguished using codes, so all reports and papers from this study will not identify your child in any way. All data associated with your and your child's private information is coded and held in a secure location at the investigator's facility at Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, and will be retained for 3 years.

14. About your child's rights, or if you have questions, who should you contact?

You can ask questions at any time about any aspect of the study that you do not understand, and the research team will answer all your questions before, during, and after the trial. If you feel that your questions have not been answered fully, or if you do not understand the content of the answers, you may continue to ask until you are satisfied by contacting:

Doctor: Li Fei

Tel.: 021-25077461

If you have questions about your child's rights, or if you would like to obtain information or provide information, or if you would like to speak with someone who is not directly involved in the study, you may contact:

Ethics Committee: Medical Ethics Committee of Xinhua Hospital, Shanghai Jiao Tong University School of Medicine

Address: No.1665, Kongjiang Road, Yangpu District

Tel: 021-25076143

Informed consent signature page

Statement of the legal guardian of the participant:

I have read and understand the information in this informed consent form. I have been given the opportunity to ask questions and I am satisfied with the answers to all questions. I have been given adequate time and opportunity to ask questions about the details of the study and to consider my child whether to participate in the study. I am voluntarily allowing my child to participate in this study. Signing this informed consent does not mean that I will waive any of my legal rights.

I have been informed that I will receive a signed copy of this document.

Name of the child (regular script): _____

Name of the parents / legal guardian (regular script): _____

Signature of the parents / legal guardian: _____

Signature Date:_____

Contact phone number: _____

Statement of the informed consent recipient :

I confirm that I have explained the details of the study, including the rights and possible benefits and risks, and give them a copy of the signed informed consent form.

Name of the informed consent recipient(regular script): _____

Signature of the informed consent recipient : _____

Signature date: _____

Contact phone number: _____