Exploring the effects of repetitive transcranial magnetic stimulation on co-morbid sleep disorders in preschool children with ADHD

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Research Article

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Abstract

Background

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neurological developmental disorders in children and sleep disorders (SD) are a common co-morbidity in children with ADHD. There are currently no pharmacological treatment options for SD in children with ADHD of preschool age (4–6 years). Repetitive transcranial magnetic stimulation (rTMS) is a novel non-invasive neuromodulation technique. This study explored the effectiveness of rTMS for co-morbid SD in preschool-aged children with ADHD.

Methods

Thirty-five children of preschool age with ADHD and co-morbid SD were recruited for this study. They met the diagnostic criteria for ADHD in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The children were divided into a parent behaviour management training (PBMT) group (n = 19) and a repetitive transcranial magnetic stimulation combined with parent behaviour management training group (n = 16). Both groups underwent eight weeks of PBMT. Children in the rTMS combined with PBMT group were given a right DLPFC low frequency stimulation intervention three times a week for the first four weeks. The children's SD levels were assessed using the Chinese version of the Children's Sleep Habits Questionnaire (CSHQ), which was measured before the start of the intervention, at the end of the eight-week intervention and four weeks after the end of the intervention, and was used to measure the effects of both intervention methods. Within-group differences were compared using a one-way ANOVA, and between-group differences were compared using an independent samples T-test.

Results

Both the PBMT group and the rTMS combined with PBMT group significantly improved the SD of preschool-aged children with ADHD (p < 0.05), but the effect of the intervention was more pronounced in the rTMS combined with PBMT group (p < 0.05) and lasted longer than the PBMT group (p < 0.05).

Conclusion

Repetitive transcranial magnetic stimulation (rTMS) is a promising non-pharmacological therapy to improve SD in preschool-aged children with ADHD.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterised by excessive amounts of inattention, hyperactivity, and impulsivity that are pervasive, impairing in multiple
ADHD is one of the most prevalent neurodevelopmental disorders, with a worldwide prevalence of about 7% (Thomas et al., 2015). In China, the prevalence of ADHD in children is about 6.26%, showing an overall high prevalence, low consultation rate, low treatment rate and underdeveloped clinical treatment capacity (Yang, 2020; Fan et al., 2022). Particularly in recent years, due to the impact of the epidemic, children with ADHD are receiving online distance learning at home, which has resulted in a lack of peer support, disruption of existing routines and excessive screen exposure, exacerbating the symptoms of children with ADHD (Thomas et al., 2020). In addition to poor academic performance, poor peer relationships, dysfunctional families, substance abuse, early sexualization, and high rates of delinquency are all common among children with ADHD (Mrug et al., 2012; Thomas et al., 2015; Yang, 2020). In addition, 15–65% of children with ADHD have symptoms that persist even into adulthood, and continue throughout their lives (Skodzik et al., 2017). This shows that ADHD is developmental and persistent and can cause immeasurable damage to the development of the child or adult.

ADHD is characterized by extremely high rates of co-morbidity, with approximately two-thirds of children with ADHD suffering from co-morbidities including, but not limited to, sleep disorders, depression, anxiety disorders, bipolar disorder, autism spectrum disorders, and delayed language function (Wolraich et al., 2019; Sciberras et al., 2022). The most prevalent co-morbidity is sleep disorders, with approximately 73% of children with ADHD suffering from sleep-related disorders, with specific symptoms including, but not limited to, difficulty falling asleep, night waking, sleep resistance, difficulty waking, daytime sleepiness, nightmares, sleepwalking, and restless legs syndrome (Owens, 2009; Sciberras et al., 2022). In addition, data has indicated a rising trend in recent years (Sung et al., 2008; Thomas et al., 2020).

The relationship between ADHD and SD appears to be bidirectional, if SD in children with ADHD is not effectively treated, this can exacerbate the core symptoms of ADHD and even bring about other developmental disorders (Grünwald & Schlarb, 2017). At the same time, it has also been suggested that the core symptoms of children with ADHD can be improved by intervening with SD in children with ADHD (Corkum, 2016). The reasons why children with ADHD are more likely to suffer from sleep disorders than their peers are complex and there are no uniform findings, but evidence has been found from neurobiological perspectives, family climate and medication side effects (Stein et al., 2012; Silk, 2019). Overall, the prevalence of SD in children with ADHD is extremely high, and if reasonable and effective interventions for SD are introduced in a timely manner, they may not only help to improve the core symptoms of ADHD, but may also reduce the chance of other co-morbidities and assist childhood development.

Current interventions for the core symptoms and co-morbidities of SD in children with ADHD have focused on both pharmacological and non-pharmacological treatments (Liu & Zhong, 2019). However, medication, which is extremely easy to build tolerance to and has some side effects, has also been reported to increase the risk of sleep disturbance in patients taking medication for ADHD (Stein et al., 2012; Grünwald & Schlarb, 2017; Fan et al., 2022). At the same time, most countries do not have FDA-
approved medications for sleep disorders in children under 16 years of age (Fan et al., 2022). This makes the use of pharmacological interventions for SD in children with ADHD in the younger age groups controversial and difficult to implement.

Among the non-pharmacological therapies are EEG biofeedback, cognitive behavioural therapy, physical exercise, and combination therapy approaches, and parental behaviour management training (Wolraich et al., 2019; Zewdie et al., 2020). Among these, parental behaviour management training (PBMT) is recommended by several manuals as well as expert consensus, recommending it as the preferred option in the non-pharmacological treatment of SD in children aged 4–6 years with ADHD (Li et al., 2019). In addition, the practice of rTMS has been well established over the years (Sugaya et al., 2022; Sciberras et al., 2022). Among the non-pharmacological treatment options, non-invasive neuromodulation techniques such as repetitive transcranial magnetic stimulation (rTMS) have received extensive research and attention in the last decade due to their high safety, efficacy and long duration of effect (Wolraich et al., 2019; Zewdie et al., 2020; Rubia, 2022). rTMS has been shown to be effective for SD in adult patients with ADHD (Gao et al., 2022; Nagy et al., 2022; Rubia, 2022). It is a promising approach to SD intervention for children with ADHD. However, there are no studies on SD interventions for preschool (4–6 years) children with ADHD (Lefaucheur et al., 2020).

This study will compare the effectiveness of parental behavioural management training, combined with parental behavioural training on repetitive transcranial magnetic stimulation for sleep disorders in children with ADHD of preschool age (4–6 years).

**Methodology**

**Participants**

Thirty-five children with ADHD who underwent parental behaviour management training at a specialist women's and children's hospital in a city in western China from June 2022 to October 2022 were selected and divided into an experimental group (rTMS combined with parental behaviour management training) and a comparison group (parental behaviour management training group) according to parents' wishes, with 16 in the experimental group and 19 in the parental behaviour management training group (see Table 1).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Age</th>
<th>Gender</th>
<th>Primary Caregiver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental group (n = 16)</td>
<td>5.16 ± 1.12</td>
<td>M = 10 F = 6</td>
<td>Parents</td>
</tr>
<tr>
<td>Comparison group (n = 19)</td>
<td>5.10 ± 1.10</td>
<td>M = 12 F = 7</td>
<td>Parents</td>
</tr>
</tbody>
</table>

Inclusion criteria: (ii) Children must meet both the diagnostic criteria for ADHD in the DSM-5 published by the American Psychiatric Association in 2013 and the diagnostic criteria for sleep disorders in the
International Classification of Sleep Disorders (3rd edition) in 2014 and the Chinese Sleep Health Guidelines for Children 0–5 years old in 2017. (ii) Age 4–6 years old, regardless of gender. (iii) Typical clinical symptoms such as sleep resistance, difficulty in falling asleep, habit of sleeping late, frequent night waking, night terrors, excessive early awakening, short sleep duration, disturbance of circadian rhythm and daytime sleepiness. (iv) No medication for ADHD, exogenous melatonin, antipsychotics, sedative and hypnotic drugs within 1 month; Informed and signed informed consent from the guardian, who voluntarily allows the child to participate in this study and whose caregiver cooperates with the study.

In this study, we need to exclude organic causes and contraindications to rTMS that may lead to sleep disorders, namely: (i) organic lesions of the brain, e.g., multiple cerebral tenderness, cerebral leukodystrophy, malformations of brain development; (ii) chromosomal or genetic abnormalities co-occurring with ASD, e.g., Rett syndrome, childhood disintegrative psychosis, Angel syndrome, fragile X syndrome, tuberous sclerosis; (iii) organic diseases of the respiratory system e.g. sleep-related breathing disorders caused by anatomical abnormalities (e.g. airway stenosis, tonsillar hypertrophy), local tissue compliance problems; (iv) people with co-morbid epilepsy; contraindications to rTMS, e.g. post-cochlear implantation, increased intracranial pressure or intracranial infection, intracranial metallic foreign bodies, etc.

The specific implementation guidelines in the Parent Behaviour Management Programme contain specific methods for managing children’s sleep, and daily actions during the training process, which need to be shared and recorded in online groups on social software, give the researcher the right to ask participating parents to withdraw from the programme if they refuse to implement it, or if they are unable to do so due to other irreversible factors. The final results will also not be included in the analysis of the experimental data.

The offline parent training for this study was conducted at the Child Psychology Department of the Experimental Hospital, and the online training was conducted on an encrypted webcast platform. All participating parents have signed an informed consent form, agreeing to participate in the experiment and to use the data as material for a non-profit scientific research project. The study was approved by the hospital ethics committee.

Assessment tools

In this study, an adapted version of the Chinese version of the Children’s Sleep Habits Questionnaire (CSHQ) was used, which is recommended by the Chinese Health Care Commission for the assessment of children's sleep problems and has good reliability (Ma & Zhong, 2022). The original version of the questionnaire contained eight dimensions: sleep resistance, delayed sleep onset, sleep duration, sleep anxiety, nocturnal awakening, heterogeneous sleep, sleep breathing disorder, and daytime sleep. These eight dimensions encompass most of the characteristics of sleep disorders in children with ADHD mentioned in the previous section. The questionnaire is based on a three-level scale with 34 questions. A
total score of more than 54 indicates that the child has a sleep disorder and requires further pathological diagnosis. The higher the score the more severe the sleep disorder.

Intervention methods

After the parents signed the informed consent form, an 8-week parental behaviour management training was conducted for the control group parents. The parental behaviour management training was conducted twice a week, the first four offline and the last four online, with the content designed by an experienced psychotherapist in conjunction with the paediatrician. After the first training was completed, parents were asked to record how they performed the child’s movements on a daily basis, as detailed in Table 2.

<table>
<thead>
<tr>
<th>Duration</th>
<th>Contents</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>One hour</td>
<td>ADHD Basics</td>
<td>Group psychological counseling room</td>
</tr>
<tr>
<td>One hour</td>
<td>ADHD and SD Basics</td>
<td>Group psychological counseling room</td>
</tr>
<tr>
<td>One hour</td>
<td>Sleep behaviour management skills (theory)</td>
<td>Group psychological counseling room</td>
</tr>
<tr>
<td>One hour</td>
<td>Sleep behaviour management skills (hands-on)</td>
<td>Group psychological counseling room</td>
</tr>
<tr>
<td>One hour</td>
<td>Parent-child communication skills</td>
<td>Online conference system</td>
</tr>
<tr>
<td>One hour</td>
<td>Sleep behaviour management skills (replay)</td>
<td>Online conference system</td>
</tr>
<tr>
<td>One hour</td>
<td>Parent-child communication skills</td>
<td>Online conference system</td>
</tr>
<tr>
<td>One hour</td>
<td>Sleep behaviour management skills (hands-on))</td>
<td>Online conference system</td>
</tr>
</tbody>
</table>

The experimental group then used rTMS in combination with parental behaviour management training for parents. rTMS was operated by the researcher in the hospital, using low frequency stimulation of the right dorsolateral prefrontal area for 20 minutes/session, 3 times/week, for 4 weeks. Parents in the experimental group attended parent behaviour management training at the same time as parents in the control group.

The specific treatment steps of rTMS are as follows: rTMS (Wuhan Eriod, model YRD.CCY-III, circular coil, frequency 1Hz) threshold determination, the first rTMS treatment requires the determination of the resting motor threshold (RMT), and the determination steps are: first, correctly wear the positioning cap, the
intersection of the naso-occipital line (the line from the root of the nose to the posterior occipital ridge) and the temporoparietal line (the line between the two zygomatic arches at the end of the depression) is the child's C2 point, ensuring that the child's C2 point coincides with the C2 point drawn on the cap. Motor-evoked potentials were then recorded using a special rTMS motor-evoked potential electrode line, with the recording electrode placed on the ventral part of the thumb short adductor muscle, the reference electrode on the distal end of the tendon and the grounding electrode on the wrist. The centre of the circular coil was positioned directly over the C2 point (stimulation of this point optimally evoked movement of the right short thumb flexor). Then, using a single pulse pattern stimulation, 10 stimulations, 5 of which evoked the thumb-split muscle movement (leading to an evoked potential of 50 µV or more in the thumb-split muscle), and the intensity of this stimulation was the resting motor threshold. Considering the stage of development of the cerebral cortex and the stage of language ability in children, a relatively low frequency treatment parameter was chosen, stimulating the right prefrontal dorsolateral area at 1 Hz with a fixed intensity of 40% x 90% x 2.88 T, 1000 pulses/second, 10 seconds of stimulation, 10 stimuli, 10 seconds of interval, 45 repetitions, and a treatment time of 20 minutes/session. To ensure accurate positioning of the rTMS coil, the child was given a positioning cap marked with an anatomically defined stimulation location and the stimulation coil was placed at 45 degrees to the surface of the child's skull with the centre of the circle placed at the stimulation point in the dorsolateral area of the right prefrontal lobe (i.e., the scalp area of F4 in the international standard EEG 10–20 system). rTMS positioning is shown in the attached Fig. 1.

Statistical analysis methods

Statistical analysis was performed using SPSS 25.0, with measures expressed as (X ± SD), a chi-square test for gender proportions, a one-way ANOVA test for within-group variation and an independent samples t-test for between-group differences. The difference was considered statistically significant at P < 0.05.

Results

The difference in gender between the two groups was not statistically significant (p > 0.05) after a chi-square test. The CHSQ is a research tool recommended by the Chinese Health Care Commission, and the recommendation manual only emphasises the significance and importance of the total score, but does not break down the specific dimensions. Therefore, only the total score was included in the statistical test in this study. After the eight-week intervention, the CHSQ scores decreased in both the experimental and comparison groups (p < 0.05), indicating that both the experimental group (rTMS combined with parental behaviour management training) and the comparison group (parental behaviour management training) achieved good results. However, the difference in scores between the experimental group and the comparison group was significant (p < 0.05), suggesting that although both programmes achieved positive results, the experimental group had a more significant intervention effect (see Table 3). A follow-up test was administered four weeks after the end of the intervention and showed that the difference between the scores of the experimental group and the initial test was still significant (p < 0.05), but the difference between the comparison group was no longer significant (p > 0.05) (see Table 4). This suggests
that rTMS combined with parental behaviour management training has better sustainability for SD in children with ADHD.

Table 3
Comparison of CHSQ group scores between different groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Pre-test(T0)</th>
<th>Post-test(T1)</th>
<th>Tracking-test(T2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental group</td>
<td>68.56 ± 8.90</td>
<td>52.50 ± 5.23</td>
<td>55.65 ± 4.54</td>
</tr>
<tr>
<td>Comparison group</td>
<td>66.42 ± 9.48</td>
<td>56.89 ± 4.63</td>
<td>62.00 ± 6.90</td>
</tr>
<tr>
<td>t</td>
<td>0.688</td>
<td>-2.638</td>
<td>-3.037</td>
</tr>
<tr>
<td>p</td>
<td>0.469</td>
<td>0.013</td>
<td>0.040</td>
</tr>
</tbody>
</table>

Table 4
Comparison of CHSQ intra-group scores by group

<table>
<thead>
<tr>
<th>Groups</th>
<th>Matching criteria</th>
<th>Standard error</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental group</td>
<td>T0-T1</td>
<td>2.31</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>T0-T2</td>
<td>2.31</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>T1-T2</td>
<td>2.31</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Comparison group</td>
<td>T0-T1</td>
<td>2.37</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>T0-T2</td>
<td>2.37</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>T1-T2</td>
<td>2.37</td>
<td>p&gt;0.05</td>
</tr>
</tbody>
</table>

Discussion

The post-test results of this trial illustrate very significantly that both groups of interventions are effective. However, rTMS combined with parental behaviour management training appears to be more effective as it not only provides greater relief of SD symptoms in children with ADHD, but also allows for a longer duration of treatment effects. The combination of multiple treatment options seems to have a very high potential for the treatment of children with ADHD compared to a single treatment option, whether it is a combination of pharmacological and non-pharmacological treatments or a combination of purely non-pharmacological treatments. As long as the combination is done in a scientific way, it can improve the various symptoms of children with ADHD significantly (Nagy et al., 2022; Pipe et al., 2022).

The DSM-5 classification of ADHD as a neurodevelopmental disorder reflects the continuity between childhood and adult mental disorders, with the diagnostic classification of childhood mental disorders being consistent with that of adults, emphasising that ADHD is a chronic mental disorder that can develop over a lifetime and requires long-term treatment (APA, 2013). Earlier identification and appropriate intervention is an important part of the treatment of ADHD. However, both direct interventions
for preschool-aged children with ADHD and interventions for their sleep disorders are very difficult. Firstly, most countries do not approve the use of medication for ADHD or sleep disorders in preschool children, and although some studies have been conducted on the effectiveness and safety of medication for preschool children with ADHD, more practice and research is needed (Sugaya et al., 2022). In addition, parents do not use medication as a first choice for children with ADHD due to concerns about side effects (Fan et al., 2022). As a non-pharmacological treatment, rTMS has become a promising option (Zewdie et al., 2020). Most trials of rTMS intervention for sleep disorder-related problems have chosen a protocol that uses low frequency stimulation on the right DLPFC (Jiang et al., 2019), and this study also chose a low frequency protocol on the right DLPFC. The reason why low frequency on the right side can help improve SD in children with ADHD is because rTMS on the right DLPFC can improve sleep by increasing serum brain-derived neurotrophic factor and GABA concentrations and decreasing motor-evoked potentials (Barahona-Corrêa et al., 2018). It has also been suggested that rTMS can decrease serum cortisol, adrenocorticotropic hormone and thyroid-stimulating hormone concentrations by modulating the function of the hypothalamic pituitary-adrenal axis and thyroid axis, while rTMS can also increase pineal melatonin secretion and brain concentrations of norepinephrine and 5-hydroxytryptamine, all of which play an important role in maintaining normal sleep rhythms (Jiang et al., 2013; Guo et al., 2017). In addition, low-frequency rTMS promotes ipsilateral hippocampal nerve regeneration and reduces apoptosis, increasing its functionality and plasticity, which also facilitates the adjustment of sleep-wake disorders (Guo et al., 2017; Rubia, 2022). rTMS has not been used for a long time in the treatment of ADHD and its co-morbidities, and reports of adverse side effects of rTMS are uncommon. Occasionally, pressure and allergy due to the device being worn on the head have been reported (Rubia, 2022). This detail was also taken into account in this study, so that the adaptation time and adjustment time for the paediatric patients was increased, and consequently no discomfort was reported by the paediatric patients or their parents during or after the treatment.

In addition, parents' or caregivers' beliefs about ADHD and its co-morbidities, as well as knowledge about them, play a crucial role in the rehabilitation and treatment of children with ADHD, both in terms of compliance and daily behavioural management, but most parents' knowledge about childhood ADHD and its co-morbidities is currently inadequate, especially in developing or relatively poor countries (Fan et al., 2022; Pipe et al., 2022; Hornstra et al., 2022). At the time of the parent behaviour management training in this study, parents reported a lack of knowledge about ADHD in relation to their co-morbidity SD, even though they exhibited proactive health care seeking behaviours. Therefore, the dissemination of knowledge about ADHD should be given attention. For example, increasing the number of lectures in primary schools or pre-schools, or even adding an assessment of ADHD and other prevalent diseases to teacher qualifications, could help teachers or caregivers to provide timely and effectively targeted help to children at an earlier stage. In addition, although many manuals recommend parental behaviour management treatments, their effectiveness is largely limited by the level of parental literacy and the level of designers and trainers, and most current manuals do not contain operational parent training methods and programmes (Hornstra et al., 2022). It is hoped that more manuals will follow with operational methods.
This study used rTMS to improve SD in preschool children with ADHD. Although some results were achieved, there are still limitations to this experiment, for example, knowledge of the specific brain mechanisms and specific pathways by which rTMS improves SD in children with ADHD, and what the effect of rTMS on specific components of sleep in children with ADHD is. In addition, issues such as parents’ own sleep habits and quality, and religious beliefs were not specifically discussed in this study. It is hoped that subsequent studies will improve on these deficiencies and bring about more meaningful advances in the treatment of children with ADHD.

Declarations

Funding

No funding was received for this study

Competing interests

No conflict of interest between all authors of this article

Ethical Affirmations

The study was approved by the Ethics Committee. All participants have signed an informed consent form agreeing to the use of the data provided for this study

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

Jiang Yilin and Zhou Heng worked together on the design and study of the experiment and their contributions were equal, with Liu Jiayang completing part of the execution of the experiment.

References

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   https://doi.org/10.3389/fnint.2018.00027


**Figures**

![Repetitive transcranial magnetic stimulation localization map and area of action](image)

**Figure 1**

Repetitive transcranial magnetic stimulation localization map and area of action