Efficacy of cerebellar transcranial magnetic stimulation in spinocerebellar ataxia type 3: A randomized controlled trial

Yuting Shi
Xiangya Hospital Central South University Department of Neurology

Guangdong Zou
Xiangya Hospital Central South University Department of Neurology

Zhao Chen
Xiangya Hospital Central South University Department of Neurology

Linlin Wan
Xiangya Hospital Central South University Department of Radiology

Linliu Peng
Xiangya Hospital Central South University Department of Neurology

Huirong Peng
Xiangya Hospital Central South University Department of Neurology

Lu Shen
Xiangya Hospital Central South University Department of Neurology

Kun Xia
Central South University School of Life Sciences

Rong Qiu
Central South University School of Computer Science and Engineering

Beisha Tang
Xiangya Hospital Central South University Department of Neurology

Hong Jiang (jianghong73868@126.com)
Xiangya Hospital Central South University

Research Article

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Abstract

Spinocerebellar ataxia type 3 (SCA3) is the most common subtype of SCA without effective treatment. This study aimed to evaluate the comparative efficacy of low-frequency repetitive transcranial magnetic stimulation (rTMS) and intermittent Theta Burst Stimulation (iTBS) in a larger cohort of SCA3 patients. One hundred and twenty patients with SCA3 were randomly selected to receive 1Hz rTMS, iTBS or sham. All patients were assessed at baseline and after all sessions. Primary outcomes included the Scale for the Assessment and Rating of Ataxia (SARA) and the International Cooperative Ataxia Rating Scale (ICARS). Secondary outcomes included 10-meter walking test (10MWT), nine-hole peg test (9-HPT), and PATA Rate Test (PRT). This study revealed that 1Hz rTMS and iTBS outperformed sham in reducing the SARA and ICARS scores in SCA3 patients, but with no difference between 1Hz rTMS and iTBS. Furthermore, iTBS decreased 9-HPT scores when using a non-dominant hand. Additionally, we found that symptom severity variance of patients did not influence the effect of rTMS on the clinical impression. No severe adverse events were recorded in this study. The study concluded that 1Hz rTMS and iTBS interventions targeting the cerebellum are effective and safe in patients with SCA3.

Introduction

The spinocerebellar ataxias (SCAs) are a group of clinically and genetically heterogeneous neurodegenerative disorders. Most often, the symptoms of these disorders begin to show in adult life. Genetically, more than 40 distinct SCAs have been defined, but spinocerebellar ataxia type 3 (SCA3) is the most common subtype. SCA3 is caused by a cytosine-adenine-guanine (CAG) trinucleotide repeat expansion in the ATXN3 gene. Despite being prevalent worldwide, SCA3 lacks an effective and safe treatment. Therefore, there is an urgent need to develop novel therapeutic strategies for SCA3.

Repetitive transcranial magnetic stimulation (rTMS), a promising non-invasive neuromodulation technique, is used to induce neuroplastic changes and promote the recovery of brain function. Many studies have reported that rTMS targeting the cerebellum could induce long-lasting changes in the functional connectivity of the cerebello-thalamo-cortical pathways. Moreover, several studies have suggested that rTMS can improve the clinical symptom of ataxia in patients with cerebellar ataxia. However, these studies focused more on low-frequency rTMS in relatively small samples of SCA3 patients, which limited a comprehensive understanding of the efficacy of cerebellar rTMS in SCA3. Meanwhile, the effect of intermittent theta burst stimulation (iTBS) on the clinical impression in patients with SCA3 has not been established.

This study aims to assess the comparative influence of 1Hz rTMS and iTBS interventions on ataxia in a larger cohort of patients with SCA3.

Materials And Methods

Experimental design and participants
This randomized and sham-controlled study was conducted between November 2019 and October 2021. We screened 182 participants with genetically confirmed SCA3. As shown in Figure 1, sixty-two were ineligible and excluded from the analysis. The remaining 120 completed baseline testing. The patients undergoing ten sessions of 1Hz rTMS, iTBS, or sham intervention participated in daily sessions for five consecutive days per week for two weeks (Mon-Fri). All patients were assessed at baseline and after all sessions. In this study, the random sequence was generated by randomization.com using randomly permuted blocks with size of six per block. Patients were blinded regarding randomization. We estimated that a total of 78 participants would be needed for a comparison among 3 independent groups, with a two-tailed α of 0.05 and a (1-β) of 0.90. Considering that the loss to follow-up of subjects was about 20%, at least 94 participants were included. After screening, 120 patients participated in this study.

Inclusion criteria were as follows: (a) SCA3 patients confirmed by genetic testing; (b) aged 18-65 years; (c) presence of ataxia with a score >3 on the Scale for the Assessment and Rating of Ataxia (SARA) and a subscore with 2-6 points on “gait”. Exclusion criteria were: (a) active infection or other pre-existing untreated medical conditions; (b) pregnancy; (c) concurrent treatment with other experimental drugs; (d) cardiac pacemakers, electronic devices, and intra-cranial metallic objects; (e) epilepsy. Written informed consent was obtained from all participants. The study was approved by the ethics committee of Xiangya hospital and registered under the Chinese Clinical Trial Registry Number ChiCTR2100046902 (http://www.chictr.org).

**Intervention**

A Magstim Rapid² (UK) with a figure-of-eight coil was used to deliver stimuli. The coil was centered over three regions: the inion, 4 cm lateral to the left, and 4 cm lateral to the right of the inion, and the handle of the coil was held facing upwards. A total of ten sessions were delivered. The 1Hz rTMS protocol consisted of 10 series of 60-sec pulses and inter-train-pulses of 1 s (for a total of 1200 pulses per session), and iTBS protocol contained 600 pulses for each cerebellar hemisphere (for a total of 1200 pulses per session). The sham stimulation was executed with a sham coil identical to active rTMS, which was positioned in the exact same way without creating a significant magnetic field.

**Outcome measures**

The primary outcomes were measured using the Scale for the Assessment and Rating of Ataxia (SARA) and the International Cooperative Ataxia Rating Scale (ICARS)¹⁰,¹¹. The secondary outcomes were examined using a 10-meter walking test (10MWT), a 9-hole peg test (9-HPT), and PATA Rate Test (PRT)¹²,¹³.

**Statistical analysis**

Analyses were performed using SPSS software version 20.0 (IBM, Armonk, NY). Descriptive statistics summarized group demographics and outcomes. Categorical variables were represented by ratio, and numeric variables by mean SD or the median (25th and 75th percentile) and compared using chi-squared
tests. On the other hand, the numeric variables were compared using t-tests. The Shapiro-Wilk test was used to evaluate the normality of data analysis, and group comparisons were conducted using Student’s t-tests and ANOVA analysis. A Friedman test was used when the variables did not present a normal distribution. Post hoc pairwise comparisons were performed as necessary with Bonferroni adjustment. A p-value less than 0.05 was considered significantly different.

**Results**

In total, 120 patients with SCA3 were recruited and randomly assigned to 1Hz, iTBS, or sham intervention, 109 of whom underwent the whole process as 11 dropped out of the study. The study flowchart is displayed in Fig 1. The demographic and clinical characteristics were similar among groups (Table 1). No between-group baseline differences were observed (Table 1 and Supplementary Table 1).

Primary and secondary outcomes were presented in Table 2. Our findings displayed that the patients receiving 1Hz rTMS intervention exhibited a slight improvement in ataxia with a 1.5-point decrease in SARA scores and a 3.8-point decrease in ICARS scores compared to baseline data (Table 2 and Fig S1). Meanwhile, patients receiving iTBS intervention presented a slight improvement with a 1.9-point decrease in SARA scores and a 4.3-point decrease in ICARS scores compared to baseline (Table 2 and Fig S2). The between-group comparison showed that 1Hz rTMS and iTBS interventions outperformed sham in reducing SARA and ICARS scores (Table 2). However, there were no significant differences in SARA and ICARS scores between the two active groups (Table 2). Additionally, the SARA and ICARS scores in the sham group did not change significantly compared to baseline, and to active rTMS groups (Table 2 and Fig S3). Regarding ICARS subscores, “kinetic function” improved slightly with statistical significance between 1 Hz rTMS and sham (p= 0.001), between iTBS and sham (p < 0.001). The subscore of “posture and gait disturbances” also improved after 1Hz rTMS intervention compared to sham (p = 0.023). After iTBS intervention, there was a trend of decrease in the subscore of “posture and gait disturbances”, although no significant difference was obtained compared to sham (p = 0.051). No other items within the ICARS were observed between groups (Table 2).

Secondary analyses revealed that 1Hz rTMS and iTBS interventions increased PATA and decreased 10MWT scores with statistical significance compared to baseline (Fig S1 and S2). However, when comparing to sham, the two active rTMS groups presented no significant differences in PATA and 10MWT (Table 2). Furthermore, patients receiving the sham intervention had no observable changes in PATA and 10MWT (Fig S3). In contrast, patients after iTBS intervention had a slight improvement in 9-HPT scores when using a non-dominant hand, as compared to baseline, to 1Hz rTMS group, and to sham respectively (Fig S2 and Table 2).

In order to determine whether symptom severity influenced the effect of rTMS on patients with SCA3, the participants were divided into mild (SARA< 10) and moderate-to-severe groups (SARA≥ 10). The results showed that symptom severity did not influence the effect of rTMS on improving the clinical impression of SCA3 patients (Fig 2).
During the trial, no patients suffered severe side effects. However, 12 of the 109 patients presented mild side effects with no between-group difference (Supplementary Table 2). Four felt mild headaches, four had mild dizziness, two had discomfort in the stimulation area of the head, one felt nausea, and one felt general discomfort during sessions.

**Discussion**

To date and our knowledge, this is the first study to investigate the efficacy and safety of rTMS in a large cohort of SCA3 patients. This trial found that patients with SCA3 who completed 2-week rTMS treatment, exhibited a slight improvement in ataxic symptoms, which were consistent with previous reports 7–9.

Particularly, the present study is the first to examine the efficacy of iTBS treatment and the comparative influence of low-frequency and high-frequency rTMS in improving the clinical symptoms of SCA3. So far, only three studies have reported the effect of high-frequency rTMS on degenerative cerebellar ataxia, including one study exploring the effect of 10 Hz rTMS in a patient with SCA6, and two studies that investigated the effect of iTBS in 50 patients with MSA, and 6 SCA38 patients respectively 14–16. Another study reported the effect of 5Hz rTMS on cerebellar ataxia in six patients with multiple system atrophy 17. Bonni S et al. suggested that iTBS, an excitatory TMS protocol, could cause clinical improvement in cerebellar stroke patients when applied to the damaged cerebellum 18. Despite the encouraging results described above, these studies had some shortcomings. The small sample sizes, variability of TMS parameters and outcome measures limit conclusions on the efficacy of cerebellar rTMS in SCA3. Moreover, the limited published studies mainly reported the effect of low-frequency rTMS on cerebellar ataxia. Especially, few studies have performed high-frequency rTMS treatment in patients with SCA3. This large-scale, randomized, controlled trial provided preliminary data that both 1Hz rTMS and iTBS interventions targeting the cerebellum were potentially effective for patients with SCA3. We acknowledge that the treatment effect in this study were relatively low despite its statistical significance. Nevertheless, these results were consistent with previous findings in which rTMS treatment was effective in cerebellar ataxia, leading to an improvement in standing posture and kinetic function, while speech and oculomotor abilities did not change significantly 7–9.

Interestingly, this study found that the low-frequency and high-frequency rTMS patterns had no significant difference in the treatment effect for SCA3. As we known, the cerebellum regulates the excitability of the primary motor cortex (M1) via the cerebellothalamocortical pathway, which is involved in cerebellar ataxia 19,20. Several studies have demonstrated that cerebellar rTMS facilitate cortical motor activation by modulating the excitability of Purkinje cells 21–23. Rodríguez-Labrada et al. proposed that low-frequency cerebellar TMS exerted its therapeutic effect in cerebellar ataxia by suppressing the Purkinje cells, resulting in the disinhibition of the contralateral M1 24. On the other hand, van Dun et al. proposed that high-frequency cerebellar rTMS resulted in clinical improvement by activating the Purkinje cells, resulting in inhibition of the contralateral M1 in cerebellar stroke patients with ataxia when applied over the damaged lateral cerebellum 19. It is known that the “inhibitory” and “excitatory” frequencies of
rTMS exert different physiological effect\(^{25}\). Notably, it is necessary to explore the possible mechanism underlying the effect of rTMS in SCA3 beyond inhibition or excitation. Besides, it has been proposed that different frequencies of rTMS change abnormal oscillations by modulating the whole brain network\(^8\).

Although all published reports showed favorable clinical outcomes of rTMS in cerebellar ataxia, there was high variability among all studies due to various factors. Generally, the geometry of the coil, various TMS paradigms, intervention targets on the cerebellum, and participants with heterogeneous genetic backgrounds play a crucial role in the effect of rTMS. The geometry of the coil is an important factor influencing rTMS efficacy. The present study used a figure-of-eight coil to stimulate the cerebellar hemispheric cortex, which has been frequently used to deliver cerebellar stimulation. The depth of the target tissue is also an important factor in TMS treatment. Considering that the distance from the scalp to the cerebellar cortex increased for patients with severe cerebellar atrophy, as well as the variance in symptom severity, this study did not include those late-stage patients with severe cerebellar atrophy. Hardwick et al. reported that figure-of-eight and double-cone coils could effectively stimulate cerebellar tissue. However, the double-cone coil is demonstrated to be the most effective in eliciting cerebellar brain inhibition (CBI) because of its much deeper stimulation\(^{26}\). Therefore, it is important to compare the effect of double-cone and figure-of-eight coils on cerebellar ataxia in future studies.

Some limitations of this study need to be considered. First, the current trial was not double-blinded, which might have yielded some bias. Second, we only performed the immediate follow-up assessment, it is meaningful to carry out longer follow-up in order to determine the duration of efficacy of rTMS in patients with SCA3. In future, long-course trials are necessary to confirm whether cerebellar rTMS is a therapeutic alternative for SCA3 patients.

**Conclusion**

This study demonstrated that the low-frequency rTMS at 1Hz and iTBS interventions are feasible and safe for patients with SCA3. These findings suggest the beneficial effects of cerebellar rTMS in SCA3.

**Declarations**

**Acknowledgments**

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Data Availability

The datasets of the current study are available from the corresponding author on reasonable request.

References


**Tables**

**Table 1.** Demographics and clinical features of each participant in this study.
<table>
<thead>
<tr>
<th></th>
<th>1 Hz rTMS n=40</th>
<th>iTBS n=40</th>
<th>Sham n=40</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>14/26</td>
<td>20/20</td>
<td>23/17</td>
<td>0.122</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40.85±10.28</td>
<td>42.23±10.19</td>
<td>43.78±7.99</td>
<td>0.379</td>
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<tr>
<td>Age at onset (years)</td>
<td>33.43±9.39</td>
<td>34.68±9.61</td>
<td>36.18±7.53</td>
<td>0.374</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>7.43±2.94</td>
<td>7.65±3.61</td>
<td>7.33±3.95</td>
<td>0.903</td>
</tr>
<tr>
<td>CAG expansion repeats</td>
<td>72.50±4.02</td>
<td>71.08±4.03</td>
<td>71.40±2.99</td>
<td>0.204</td>
</tr>
</tbody>
</table>

Notes: Values are mean ± SD or n (%). Abbreviations: rTMS: repetitive transcranial Magnetic stimulation, iTBS: intermittent theta burst stimulation.

**Table 2.** Differences of outcome measures before and after active rTMS and sham interventions.
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>1 Hz rTMS n=38</th>
<th>iTBS n=34</th>
<th>Sham n=37</th>
<th>P value</th>
<th>1 Hz rTMS vs sham</th>
<th>iTBS vs sham</th>
<th>1 Hz rTMS vs iTBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARA</td>
<td>-1.47±1.21</td>
<td>-1.92±1.50</td>
<td>0.05±1.10</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.343</td>
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<tr>
<td>ICARS</td>
<td>-3.79±3.35</td>
<td>-4.27±3.43</td>
<td>-0.19±2.74</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>1.000</td>
</tr>
<tr>
<td>Posture and gait disturbances</td>
<td>-1.34±1.38</td>
<td>-1.24±1.79</td>
<td>-0.41±1.24</td>
<td>0.014</td>
<td>0.023</td>
<td>0.051</td>
<td>1.000</td>
</tr>
<tr>
<td>Kinetic functions</td>
<td>-2.00±2.71</td>
<td>-2.73±2.27</td>
<td>0.24±2.54</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>0.986</td>
</tr>
<tr>
<td>Speech disorders</td>
<td>0.00 0.00</td>
<td>0.00 0.00</td>
<td>0.00 0.00</td>
<td>0.581</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oculomotor disorders</td>
<td>0.00 -1.00</td>
<td>0.00 -1.00</td>
<td>0.00 0.00</td>
<td>0.306</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>10MWT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine speed</td>
<td>-0.50 -1.18</td>
<td>-0.33 -1.25</td>
<td>-0.20 -0.77</td>
<td>0.069</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fastest speed</td>
<td>-0.16 -0.67</td>
<td>-0.39 -1.21</td>
<td>-0.05 -0.35</td>
<td>0.439</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9-HPT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant hand</td>
<td>-1.32 -4.01</td>
<td>-0.42 -3.20</td>
<td>-0.51 -2.18</td>
<td>0.682</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Non-dominant hand</td>
<td>-1.03±6.41</td>
<td>-2.77±3.66</td>
<td>0.57±4.77</td>
<td>0.020</td>
<td>0.560</td>
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<td>PRT</td>
<td>0.50 0.00</td>
<td>1.00 0.00</td>
<td>0.50 -0.25</td>
<td>0.563</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Notes: Values are mean ± SD or median (interquartile range). Abbreviations: rTMS: repetitive transcranial magnetic stimulation, iTBS: intermittent theta burst stimulation, SARA: Scale for the Assessment and Rating of Ataxia, ICARS: International Cooperative Ataxia Rating Scale, 10MWT: 10 meters walking test, 9-HPT: nine-hole peg test, and PRT: PATA Rate Test.

Figures
Figure 1

Study flow. Schematic flow chart illustrates recruitment, group allocation, treatment, and analysis.
Figure 2

Assessment of ataxia for patients with SCA3 between the mild and moderate-to-severe groups after 1Hz rTMS or iTBS intervention. (A) changes of the Scale for the Assessment and Rating of Ataxia (SARA) (B) and International Cooperative Ataxia Rating Scale (ICARS) scores after 1Hz rTMS; (C) changes of SARA and ICARS (D) scores after iTBS.

Supplementary Files

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