Brain Stimulation xxx (2018) 1–9

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

# Efficacy of repetitive transcranial magnetic stimulation for Tourette syndrome: A systematic review and meta-analysis

Chih-Wei Hsu [a], Liang-Jen Wang [b, c], Pao-Yen Lin [a, d, *]

[a] Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan
[b] Department of Child and Adolescent Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan
[c] Department of Chinese Medicine, College of Medicine, Chang Gung University, Taoyuan, Taiwan
[d] Institute for Translational Research in Biomedical Sciences, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

ARTICLE INFO

*Article history:*
Received 17 February 2018
Received in revised form
28 May 2018
Accepted 1 June 2018
Available online xxx

*Keywords:*
Brain stimulation
Meta-analysis
rTMS
Tic disorder
Tourette syndrome
Transcranial magnetic stimulation

ABSTRACT

*Background:* While previous studies have investigated the effect of repetitive transcranial magnetic stimulation (rTMS) in treating Tourette syndrome (TS), the results remain inconclusive.
*Objective:* We aim to systematically review the existing literature related to the efficacy of rTMS in TS and synthesize the results through meta-analysis.
*Methods:* We searched for PubMed, Embase, Cochrane Library, and ClinicalTrials.gov databases without language restriction through January 1, 2018, and included randomized-controlled and open-label trials that assessed the treatment effect of rTMS for tic symptoms. We used a random-effects model to pool effect sizes, which were expressed as Hedges' $g$ and 95% confidence intervals (CIs). The outcomes include symptom improvement of tic, obsessive-compulsive (OC), and attention-deficit hyperactivity disorder. Distribution of sex, age, and differences of rTMS protocol were examined as potential moderators.
*Results:* Eight studies were included in the meta-analysis. rTMS significantly improved tic ($g = -0.61$; CI: $-0.94$ to $-0.29$) and OC ($g = -0.48$; CI: $-0.83$ to $-0.14$) symptoms in TS patients, compared to baseline. However, active rTMS was not effective in tic or OC symptoms among patients with TS when controlled for placebo. Furthermore, stimulation of the bilateral supplementary motor areas was more effective in tic symptoms than that of other areas ($g = -0.70$; CI: $-1.11$ to $-0.30$ vs. $g = -0.36$; CI: $-0.84$ to 0.14). Moreover, a younger age was associated with a better treatment effect (coefficient = 0.03, $p = 0.027$).
*Conclusion:* Current study indicates that rTMS has a significant effect on tic and OC symptoms in TS patients.



## 1. Introduction

Tourette syndrome (TS) is a predominantly male childhood-onset condition characterized by motor and vocal tics [1] and affects 0.77% of the population [2]. While tics are rarely detrimental, they are often perceived as bothersome and disruptive [3] and may hinder effective learning and social interactions [4]. In recent decades, comprehensive behavioral intervention for tics (CBIT) has been a safe and effective treatment for tic symptoms, but it requires time to train skilled practitioners. Furthermore, with a positive response in roughly half of the subjects, it may be limited as a treatment for tics [5]. Antipsychotic agents have also exhibited strong data with regard to tic symptoms, but their use is often limited in children and adolescents due to their potential side effects [6]. Although some other pharmacologic treatments for TS are available, such as α2-adrenergic receptor agonists (clonidine) [7] and vesicular monoamine transporter type 2 (deutetrabenazine) [8], the sedative effect (clonidine) and high percentage of side effects (deutetrabenazine: 65.2%) currently pose challenges in clinical practices [8,9]. Therefore, other safe and effective interventions are needed to treat tic symptoms.

Transcranial magnetic stimulation (TMS) is a brain neuromodulation technique that uses a changing magnetic field to cause electric current flow in a focal cortical area via electromagnetic

* Corresponding author. Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital, No.123, Dapi Road, Niaosong District, Kaohsiung City, 833, Taiwan.
*E-mail address:* py1029@adm.cgmh.org.tw (P.-Y. Lin).

https://doi.org/10.1016/j.brs.2018.06.002
1935-861X/

induction [10]. Repetitive TMS (rTMS) delivers repeated single magnetic pulses to the brain, which interact with originally spontaneous oscillatory rhythms in the cortical circuits and then induce an activity-dependent plasticity according to phase-locking synchrony between pattern of the stimulation and oscillation of the brain [11]. Finally, the approach may offer an alternative to pharmacological treatments of various neuropsychiatric disorders. Several meta-analysis studies have indicated that rTMS can effectively treat psychiatric and movement disorders in adults, such as major depressive disorder (MDD) [12], obsessive-compulsive disorder (OCD) [13], and Parkinson disease (PD) [14]. rTMS has also been extended to treat disorders that start in childhood and adolescence, such as autism spectrum disorder (ASD) [15] or attention-deficit hyperactivity disorder (ADHD) [16]. In the past decade, rTMS has been studied for its efficacy in treating TS [17,18].

rTMS has been shown to be a safe modality for TS in children and adolescents, corresponding with similar incidence of adverse events in adults [19]. Regarding its effectiveness in TS patients, an increasing amount of research has explored the changes in tics after rTMS, and several descriptive reviews have suggested that rTMS may potentially be an emerging treatment for TS [20]. However, to the best of our knowledge, no meta-analysis has currently summarized evidence about the efficacy of rTMS in TS. Furthermore, some questions have yet to be answered. First, approximately 30% and 65% of TS patients meet the diagnostic criteria for OCD and ADHD, respectively [21]. However, whether rTMS can treat symptoms of OCD or ADHD in TS patients remains unknown. Second, whether the efficacy of rTMS for tic symptoms is associated with patients' gender and age is still poorly understood. Finally, differences in rTMS protocols may influence the treatment outcome of tic symptoms.

To examine the efficacy of rTMS in TS, we performed this meta-analysis to investigate whether rTMS can improve tic, OCD, and ADHD symptoms. We also survey certain covariables that may affect clinical efficacy.

## 2. Material and methods

### 2.1. Search strategy and study selection

This report adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Supplemental Tables 1) [22]. We searched for PubMed, Embase, and the Cochrane Library without language or species restrictions from inception through January 1, 2018. These electronic databases were searched using combinations of the following terms: [tic* OR "tic disorder*" OR Tourette*] AND ["transcranial magnetic stimulation*" OR "theta burst stimulation*"]. Furthermore, we searched additional databases at clinicaltrials.gov (www.clinicaltrials.gov) for ongoing clinical trials and manually screened the reference lists of previous reviews on TMS for tic disorder OR Tourette. Two independent authors (LJW and CWH) first separately screened the titles and abstracts and then identified potentially eligible articles to be included in the meta-analysis. Any inconsistencies were resolved using a consensual approach. If a disagreement could not be resolved, we consulted a third reviewer (PYL) for the final decision. We included clinical trials that met the following criteria: (1) the subjects are patients diagnosed with TS or tic disorders (TD); (2) the procedure is rTMS or theta burst stimulation (TBS); and (3) the outcome includes the assessment of tic symptoms. We excluded the following types of studies: (1) reviews, case reports, animal studies, and conference abstracts or presentations and (2) overlapping publications. We summarized the selection process in the PRISMA flowchart (Fig. 1).

### 2.2. Data extraction and quality assessment

One author (CWH) performed data extraction, while the others (LJW and PYL) checked for accuracy. The data that we extracted from the selected studies mainly included study design, patient characteristics (diagnosis, sample number, sex, age, ethnicity, and medication), treatment parameters (type of sham, treatment site, motor threshold, frequency, and total number and sessions of stimuli), and outcome measurements (time to evaluation and rating scale). We were particularly interested in the severity of tic symptoms, which was measured using the Yale Global Tic Severity Scale (YGTSS), including motor and vocal tics along five dimensions (number, frequency, intensity, complexity, and interference) and tic-related impairment (self-esteem, family life, social acceptance, and performance) [23], and the Motor tic, Obsessions and compulsions, Vocal tic Evaluation Survey (MOVES) [24], so we extracted the scores from the included studies. Since patients with TS usually have comorbid OCD or ADHD symptoms, we also recorded the Yale-Brown Obsessive-Compulsive Scale (YBOCS) [25] and the Children's Yale-Brown Obsessive-Compulsive Scale (CYBOCS) [26], and DuPaul ADHD Rating Scale (DARS) [27], Swanson, Nolan, and Pelham-IV Rating Scale for ADHD (SNAP-IV) [28], and ADHD Self-Report Scale (ASRS) [29] in these articles, respectively. Furthermore, if a number of rating scales were used to assess tic symptoms in a single study, we gave preference to the YGTSS because it had better internal consistency and divergent validity than MOVES [30] and was used more frequently (8 in 9 studies) in comparison to MOVES (2 in 9 studies). If a study had missing or unclear rating scales, we contacted the authors of the original studies for further information.

We evaluated the quality of the included non-randomized and randomized studies using the Newcastle-Ottawa scale and Jadad scale, respectively [31,32]. The Newcastle-Ottawa scale judges each study on eight items in three domains and assigns a maximum of nine points. Scores of 7–9 indicate a good-quality study; scores of 4–6 indicate a fair-quality study; and scores of 3 or lower indicate a low-quality study. The Jadad scale evaluate three items using a scale that ranges from 0 to 5 points; a study with a score less than 3 points is considered to have a flawed methodology. The details of the quality assessment are summarized in Supplemental Tables 2 and 3.

### 2.3. Data synthesis and statistical analysis

The effect size (ES) of improvement in tic symptoms, which is derived from pre- and post-rTMS scores of YGTSS, was the primary outcome. Some trials evaluated YGTSS more than once after final TMS, so we defined the "post-" score as the closest evaluation after the rTMS protocol was completed. Since two parallel design trials presented YGTSS scores from sham control groups, we also analyzed the ES of these trials for adjustment placebo effect. Furthermore, the ES of OCD or ADHD symptom changes was regarded as the secondary outcome, which was analyzed with the same definition of the primary outcome. Finally, we used Hedges' $g$ and 95% confidence intervals (95% CIs) to estimate the ESs. A negative ES value indicated the favorable treatment of those symptoms through rTMS. Due to the presumed heterogeneity of different treatment regimens and sample populations, we adopted a random-effects model for meta-analyses throughout this systematic review. We used the Cochran's Q test and I-square to assess the heterogeneity of the tic symptom data. Upon identifying substantial heterogeneity, we performed subgroup analysis (random-effect model) or meta-regression analysis (maximum likelihood method) to investigate potential

Please cite this article in press as: Hsu C-W, et al., Efficacy of repetitive transcranial magnetic stimulation for Tourette syndrome: A systematic review and meta-analysis, Brain Stimulation (2018), https://doi.org/10.1016/j.brs.2018.06.002