Review article

Comparison of efficacy of deep brain stimulation, repeat transcranial magnetic stimulation, and behavioral therapy in Tourette syndrome: A systematic review and Bayesian Network Meta-Analysis

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ABSTRACT

Background: Tourette syndrome (TS) is an incurable neuropsychiatric disorder. Deep brain stimulation (DBS), repeat transcranial magnetic stimulation (rTMS), and behavioral therapy (BT) are all effective treatments. However, the comparison of therapeutic effect of these three therapies is lacking.

Methods: A systematic literature search was conducted for randomized controlled studies (RCT). A network meta-analysis by R4.04 software according to Bayesian framework were performed. Results were meta-analyzed and network meta-analyzed to evaluate and compare the efficacy of DBS, rTMS and BT in TS patients.

Results: A total of 18 randomized controlled studies with 661 participants were included. The Yale Global Tic Severity Scale (YGTSS) and the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) were utilized to evaluate the symptoms of TS. All three treatments improved the tic symptoms of TS [DBS 12.11 (95%CI 7.58–16.65); rTMS 4.96 (95%CI 1.01–10.93); and BT 11.72 (95%CI 10.42–13.01)]; and obsessive-compulsive symptom [DBS 4.9 (95%CI 1.13–8.67); rTMS 5.28 (95%CI 0.21–10.77); and BT 1.61 (95%CI 0.74–2.48)]. The cumulative probability results showed that DBS had the best effect on the improvement of tic symptoms, followed by BT; and rTMS was ranked last. However, in terms of improvement of obsessional symptoms, rTMS was ranked first, DBS was ranked second, and BT was ranked last. In addition, the meta regression analysis of YGTSS in DBS, rTMS and BT has significant difference (P = 0.05).

Limitation: Due to the lack of quantitative indicators, we did not perform a network meta-analysis of the side effects of the three treatments.

Conclusion: Our study showed that DBS, rTMS, and BT are effective in TS. DBS causes the best improvement in tic symptoms, and rTMS is the most effective in improving the obsessive-compulsive symptoms.

1. Introduction

Tourette syndrome (TS) is a kind of neuropsychological disease characterized by motor and vocal tics. Tics is one of the major symptoms of TS. The onset of TS is typically during early childhood, and the symptoms are gradually relieved during adolescence [1, 2]. However, a significant proportion of TS patients suffer from obvious symptoms during their entire period of life [3, 4]. The pathological l of TS is conceptualized as a basal ganglia disorder [5, 6]. About 85% of TS patients have psychiatric behavioral complications, including attention deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD) [7, 8, 9].

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Currently, the main treatment methods of TS include drug therapy, behavioral therapy (BT), and surgical therapy [10, 11, 12, 13]. Drug therapy mainly includes α-adrenergic receptor agonists, antipsychotics, benzodiazepines, and botulinum toxin [3, 14, 15], which have obvious efficacy, but they also have side effects and intolerance. Recently, many studies have shown that non-drug therapy, such as deep brain stimulation (DBS), repeat transcranial magnetic stimulation (rTMS), and behavioral therapy, also improve TS significantly [16].

DBS is an invasive technology in which an electrode is implanted in specific nuclei in the brain to suppress the abnormal electrical activity of neurons. Many positive evidences have shown that DBS can improve the motor and non-motor symptoms [17, 18, 19]. Because DBS is not currently approved by the FDA for tics, the recommended indications are severe tics and poor symptom relief despite the use of at least three different classes of medication [20].

rTMS is a safe and non-invasive therapeutic method, which is widely used in Psychoneurosis disorder [21]. Many studies have shown that the supplementary motor area is an effective target for rTMS [22, 23]. Compared to pure TS patients, rTMS is more effective in patients who have comorbidities with ADHD and/or OCD [24].

Habit reversal training and tic integrated behavioral intervention are collectively called BT [25]. Habit reversal training includes awareness training and competitive response training, self-monitoring, relaxation training, emergency management, motivational procedures, and generalization training [26]. BT has been shown to be effective in reducing the severity of tics [27, 28, 29].

Currently, the treatment of TS includes the following three stages: first, psychological education and social support for mild patients and their families; second, active drug and behavioral intervention; and third, invasive or non-invasive neuromodulation, such as DBS and rTMS, is used in patients with severe and medically refractory TS [10]. In clinical practice, it is important to synthesize empirical evidence to guide clinical decision-making. Meta-analyses provide a quantitative synthesis of treatment trials and can examine and assess the treatment outcomes between treatments. Thus, we aimed to compare the efficacy of the three above-mentioned therapies.

2. Methods

A meta-analysis was conducted following the PRISMA guidelines (supplemental file 1).

Search Strategy: We searched the PubMed, EMBASE, Cochrane Library, and Web of Science databases for randomized controlled studies (published before October 2020; no language restrictions). The search formula used in PubMed was as follows: tics [Title/Abstract] OR tic disorder [Title/Abstract] OR Tic Disorders [Title/Abstract] OR Tourette [Title/Abstract] OR Tourette Syndrome [Title/Abstract] OR Tourette’s Syndrome [Title/Abstract] OR Gilles de la Tourette syndrome [Title/Abstract] OR tic movements [Title/Abstract] AND (Deep Brain Stimulations [Title/Abstract] OR Brain Stimulation*, Deep [Title/Abstract] OR Deep Brain Stimulation*[Title/Abstract] OR Stimulation*, Deep Brain [Title/Abstract] OR Electrical Stimulation of the Brains [Title/Abstract]); (((tics [Title/Abstract]) OR (tic disorder [Title/Abstract])) OR (Tic Disorders [Title/Abstract])) OR (Tourette [Title/Abstract])) OR (Tourette’s Syndrome [Title/Abstract]) OR (Tourette Syndrome [Title/Abstract]) AND (((behavioral therapy [Title/Abstract]) OR (comprehensive behavioral intervention for tics [Title/Abstract]))) OR (((tics [Title/Abstract]) OR (tic disorder* [Title/Abstract]) OR (Tourette [Title/Abstract])) OR (Tourette Syndrome [Title/Abstract]) OR (Tourette’s Syndrome [Title/Abstract]) OR (Gilles de la Tourette

Figure 1. The PRISMA diagram of study selection.
syndrome [Title/Abstract]) AND (((transcranial magnetic stimulation [Title/Abstract]) OR (repetitive transcranial magnetic stimulation [Title/Abstract])) OR (theta burst stimulation [Title/Abstract])) OR (rTMS [Title/Abstract])) OR (TMS [Title/Abstract])) (supplemental file 2). In addition, we searched the references for relevant literature to ensure that no literature was missed out.

2.1. Study selection and data extraction

**Inclusion criteria:** (1) Subject: Diagnostic Criteria for Tourette syndrome: Diagnostic Manual of Mental Disorders, 4th Edition. (2) Intervention: DBS or rTMS or BT. (3) Follow-up time: no limitation. (4) Type of study: randomized controlled trials. (5) The results of the study: YGTSS or Y-BOCS

**Exclusion criteria:** (1) Review. (2) Data were lost or could not be extracted. (3) Animal experimental research, case report, and open label experiment. (4) Repeatedly published patient data.

**Quality assessment and data extraction.** We used the Cochrane collaboration tool to assess the risk of bias in randomized controlled trials, mainly focusing on seven areas of the risk of bias. (1) Sequence generation; (2) Allocation concealment; (3) Participants unaware of the situation; (4) No knowledge about the result evaluation; (5) Incomplete outcome data; (6) Selective result report; and (7) Other bias. The name of the first author, year of publication, sample size, patient age, duration of illness, and outcome measure were selected from these articles. Two independent researchers selected studies by investigating the title and abstract of each article and extracted data of the article that met the inclusion criteria. To obtain missing data, we will first attempt to contact the authors by e-mail. Otherwise, the data will be verified from other trials in the network or from other published meta-analyses.

**Efficiency measures:** The Yale Global Tic Severity Scale (YGTSS) was used to evaluate the severity of motor and vocal tics, including five dimensions, such as quantity, frequency, intensity, complexity, and interference. Higher the score of YGTSS, worse the symptom of tics. The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) was used to evaluate the presence and severity of compulsive behavior, including obsessive thinking and behavior. The score increased with the severity of OCD. We use the mean difference and 95% confidence interval to represent the

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Table 1. The characteristics of included article.

| Intervention | Authors & Year          | Total No. of Patients | No. of Patients Included | Sex (male No./total) | Education, yrs | Age, mean, yrs | Duration of disease, mean, yrs | Target | ui/bi | Follow-up period |
|--------------|-------------------------|-----------------------|--------------------------|---------------------|----------------|----------------|-------------------------------|--------|------|------------------|
| DBS          | Marie-Laure Welter et al, [40] 2017 | 19 16/16 NA 30.8 | 16 | 12/16 | NA | 30.8 | NA | GPI | bi | 12 months |
|              | Kefalopoulou et al, [41] 2015 | 15 | 15 | 11/15 | NA | 34.7 | NA | GPI | bi | 16 - 7 months |
|              | schoenberg et al, [42] 2014 | 5 | 5 | 1 | 13.8 | 28.2 | NA | thalamus | bi | 3 months |
|              | Michael S. Okun et al, [43] 2013 | 5 | 5 | 2/5 | NA | 33.4 | 28.8 | thalamus | bi | 6 months |
|              | Ackermans et al, [44] 2011 | 8 | 6 | 6/6 | NA | 40.33 | 33 years | thalamus | bi | 12 months |
|              | Marie-Laure Welter et al, [45] 2008 | 3 | 3 | 1/3 | NA | 32 | 23 | thalamus and GPI | bi | 20-60months |
|              | MACIUNAS et al, [46] 2007 | 10 | 5 | 5/5 | 13.8 | 28.2 | 10.4 (age) | thalamic | bi | 3 months |
| rTMS         | Landeros-Weisenberger et al, [47] 2015 | 20 | 16 | 4/16 | NA | 29.1 | NA | SMA | bi | 6 weeks |
|              | Wu et al, [48] 2014 | 13 | 12 | 9/12 | NA | 13.5 | 8.5 | SMA | bi | NA |
|              | orth et al, [49] 2005 | 5 | 5 | 4/5 | NA | 29 | NA | PMC | bi | NA |
|              | Chae et al, [50] 2004 | 8 | 8 | 5/8 | NA | 34.9 | 28.4 | left PFC | ui | NA |
| BT           | Joseph F. McGuire et al, [51] 2020 | 122 | 113 | 78/122 | NA | 31 | NA | / | / | 6 months |
|              | Ricketts et al, [52] 2016 | 25 | 20 | 13/20 | NA | 12.16 | NA | / | / | NA |
|              | Himle et al, [53] 2012 | 20 | 18 | 33/36 | NA | 8-17 | NA | / | / | 4 months |
|              | Piacentini et al, [54] 2012 | 126 | 126 | 99/126 | NA | 11.6 | NA | / | / | 6 months |
|              | Wilhelm et al, [55] 2012 | 177 | 113 | 78/122 | NA | 16-69 | NA | / | / | 6 months |
|              | Deckersbach et al, [56] 2006 | 35 | 30 | 15/28 | 14.9 | 35.1 | 7.5 | / | / | 6 months |
|              | Verdellen et al, [57] 2004 | 45 | 43 | 34/43 | NA | 20.6 | 6.8 | / | / | 3 months |

Abbreviations: DBS, deep brain stimulation, rTMS, repeat transcranial magnetic stimulation, BT, behavior therapy, NA, no applicable, GPI, globus pallidus internus, SMA, supplementary motor area, rTMS, repeat transcranial magnetic stimulation, BT, behavioral therapy, PMC, pre-motor cortex, PFC: prefrontal cortex, ui, unilateral, bi, bilateral.
result, such as 12.11 (95% CI 7.58–16.65). It refers to mean difference is 12.11, and 95% CI is 7.58–16.65.

**Statistical analysis:** We used RevMan and version 5.3 from the Cochrane Library for routine paired unit analysis. A network meta-analysis using the coda package (CRAN - Package coda (r-project.org), version 0.19–4), lattice package (CRAN - Package coda (r-project.org), version 0.19–4) and GeMTC package (https://cran.r-project.org/web/packages/gemtc/index.html, version 1.0.1) in R, version 4.04 [30]. The efficacy was compared by the YGTSS and Y-BOCS, and it was reported as the mean difference and 95% credibility interval, with a significance level of 0.05. A forest plot presented the efficacy, including the direct and indirect comparison. In addition, we evaluated the rank probability via surface under the cumulative ranking (SUCRA), a higher rank probability value indicated a more desirable attribute relative to the endpoint [31]. To compare consistent and inconsistent models, we will use the Bias Information Criterion (DIC). DIC provides a measure of model fit that penalizes model complexity; lower DIC values indicate better model fit, and the difference between the two models is substantial. In addition, the p-value of the node split analysis is derived by comparing the direct and indirect estimates and can be used to assess the consistency of the network. p < 0.05 will be used to indicate significant inconsistency [32]. The heterogeneity of the included studies was evaluated according Cochrane’s chi-square statistics and I² and publication bias was investigated via Deeks’ funnel plot [33].

3. Results

A total of 888 articles were identified from the initial researches, and 98 articles were removed because of duplication. Based on the titles and abstracts, 744 articles were considered irrelevant literature and excluded (Figure 1). Further, 28 articles were excluded through full text screening. Finally, a total of 18 articles including 661 patients were included to compare the effects of BT, DBS, and rTMS. These 18 studies were published between 2004 and 2019. The characteristics of each article are...
shown in Table 1. Figure 2 shows the network of eligible comparisons for the outcome. The included studies were evaluated using the risk of bias summary and graph (Figure 2).

3.1. Traditional meta-analysis

**YGTSS:** Compared with the baseline, DBS significantly decreased the YGTSS score (12.11 [7.58, 16.65]) with light heterogeneity ($I^2 = 30\%$). There was a significant YGTSS score reduction after BT (11.72 [10.42, 13.01]) with mild heterogeneity ($I^2 = 58\%$). rTMS decreased the YGTSS score (4.96 [1.01, 10.93]) with no heterogeneity ($I^2 = 0\%$) (Figure 3A).

**Y-BOCS:** Compared with the baseline, rTMS caused significant reduction in the Y-BOCS score with no heterogeneity ($I^2 = 0\%$). DBS also significantly decreased the Y-BOCS score (4.9 [1.13, 8.67]) with no heterogeneity ($I^2 = 0\%$). BT reduced the Y-BOCS score (1.61, [0.74, 2.48]) with high heterogeneity ($I^2 = 90\%$) (Figure 3B).

We also evaluated the improvement of tics, including motor, phonic and impairment in the score of YGTSS. As is shown in Figure 4, DBS, rTMS and BT improve the motor symptom (DBS 3.87 [1.84, 5.89]; rTMS 0.80 [−1.79, 3.39]; BT 4.25 [1.53, 6.97]) and phonic symptom (DBS 3.42 [−0.30, 6.55]; rTMS 0.40 [−3.21, 4.01]; BT 3 [−1.81, 7.81]). The impairment also improved in DBS and BT (DBS 11.54 [5.31, 17.78]; BT 10.42 [3.51, 17.33]). The included studies of BT containing child and...
adult, so we conducted a subgroup analysis of children and adults in BT. BT is both effective in child (12.47 [10.03, 14.91]) and adult (11.42 [9.90, 12.95]). In addition, there was no significant difference in the subgroup differences (p = 0.47) (Figure 4).

Some DBS subjects included in the DBS analysis had already failed CBT, so we excluded these subjects and conducted Traditional meta-analysis, with the results as follows. Compared with the baseline, DBS significantly decreased the YGTSS score (8.82 [2.98, 14]) with no heterogeneity (I² = 0%) (Figure 5A). DBS also significantly decreased the Y-BOCS score (5.60 [2.08, 10.12]) with no heterogeneity (I² = 0%). Excluding subjects enrolled in DBS after BT treatment failure, DBS still improved YGTSS, but did not improve YBOCS (Figure 5B). DBS also significantly reduced YGTSS scores after 12 months of follow-up (Figure 5C).

### 3.2. Network meta-analysis

**YGTSS**: Compared with the baseline, the mean difference was as follows: BT 14.7 (−6.33, 17.13); DBS 18.27 (15.22, 21.32); and rTMS 6.27 (−6.69, 20.07). Only DBS appeared to be more effective compared with the situation at baseline. However, there was no significant difference among the three types of intervention, BT (BT vs DBS 4.42 [1.34, 12.08]; BT vs rTMS 1.77 [0.18, 3.36]); DBS vs rTMS 11.71 [6.54, 16.88]) (Table 2).

### Table 2

| Study or Subgroup | Baseline | Mean [SD] | Total | Mean [SD] | Weight | IV, Fixed, 95% CI | Mean Difference | IV, Fixed, 95% CI |
|------------------|----------|-----------|-------|-----------|--------|------------------|-----------------|-----------------|
| Study or Subgroup | Baseline | Mean [SD] | Total | Mean [SD] | Weight | IV, Fixed, 95% CI | Mean Difference | IV, Fixed, 95% CI |
| 1.4.1 DBS        |          |           |       |           |        |                  |                 |                 |
| Kelakoupyou et al 2015 | 22.3 | 2 | 17.9 | 6.1 | 13 | 20.9% | 6.00 [11.36, 15.86] | 0.47 [1.34, 12.08] |
| Michael S. Oskin et al 2013 | 23.6 | 2.1 | 20.5 | 3.4 | 5 | 15.4% | 2.00 [10.70, 30.0] | 0.42 [1.14, 3.8] |
| Subtotal (95% CI) |          |           |       |           |        |                  |                 |                 |
|                |          |           |       |           |        |                  |                 |                 |
| 1.4.2 DBS        |          |           |       |           |        |                  |                 |                 |
| or/DBS           | 14.4 | 2.7 | 13.4 | 1.5 | 5 | 22.0% | 1.00 [11.36, 15.86] | 0.47 [1.34, 12.08] |
| Subtotal (95% CI) | 16.2 | 2.7 | 13 | 1.5 | 5 | 22.0% | 1.00 [11.36, 15.86] | 0.47 [1.34, 12.08] |
| Heterogeneity: CH² = 0.03, df = 1 (P = 0.85), I² = 0% |          |           |       |           |        |                  |                 |                 |

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**Figure 4.** Forest plots of mean difference of motor(A), phonnic(B) and impairment(C) in YGTSS. The forest plots of child(C) and adult(D) in BT. SD, standardized mean, CI, confidence interval, DBS, deep brain stimulation, rTMS, repeat transcranial magnetic stimulation.
Compared with the baseline, the mean difference was as follows: BT 1.72 (0.14, 3.29); DBS 4.89 (1.04, 8.74); and rTMS 5.38 (-0.52, 10.80). BT and DBS appeared to be more effective compared with the situation at baseline. There was no significant difference among the three types of intervention (BT vs DBS 3.17 (-0.92, 7.43); BT vs rTMS 3.67 (-2.36, 9.38); DBS vs rTMS 0.39 (-6.84, 7.12)) (Table 2).

3.3. Grade probability and SUCRA

The grade probability of YGTSS showed that DBS was ranked the highest (SUCRA = 66.7%), followed by BT and rTMS, which were ranked second and third, respectively (SUCRA = 37.5%) (Figure 6A). In Y-BOCS, rTMS was ranked the highest (SUCRA = 64.5%), DBS was ranked second (SUCRA = 62.5%), and BT was ranked third (SUCRA = 21.7%) (Figure 6B). The funnel plot showed evidence for publication bias, with similar studies on both sides of the funnel plot, suggesting that no publication bias was observed (Figure 6C, D).

3.4. Consistency and convergence analysis

For eliminating heterogeneity, sensitivity analysis was conducted, but the pairwise meta-analysis of Y-BOCS after BT was failed. To further explore the source of heterogeneity, we conducted a meta-regression analysis for the age, gender and baseline characteristic of the included patients and fortunately no heterogeneity was found (Figure 7). Further construction of the consistency model and the inconsistency model identified that the difference in the deviance information criterion between the two was less than 5 (Supplementary file S3). The potential scale reduction factor (PSRF) values of all parameters were limited to 1, which demonstrated good convergence and efficiency.

4. Discussion

Our results demonstrated that BT, DBS, and rTMS are significantly effective in treating TS. Furthermore, DBS is more effective in improving...
the tic symptoms of TS and rTMS is more effective in improving the obsessional symptoms.

Many previous studies have also shown that BT, DBS, and rTMS have therapeutic function in TS [2, 3, 10]. However, there is no study comparing the efficacy of these three treatments [34]. These treatments play a different function in clinical practice. BT has been the most widely used in recent years, mainly because of a mild adverse effect and obvious efficacy [27, 35]. Nevertheless, rTMS and DBS, which were regarded as neuromodulation methods, are utilized in patients with refractory TS, and these methods have more severe side effects than BT. The risks and adverse reactions of DBS operation, such as infection and bleeding, limit its application. Compared to DBS, rTMS has a less serious side effect of which most common is headache. Hence, it is quite necessary to compare the efficacy of these treatments.

Our study is the first network meta-analysis to compare the efficacy of BT, DBS, and rTMS in patients with TS. The disease heterogeneity in TS

Figure 6. SUCRA plots for the outcome ‘Y-BOCS’ (A) and ‘YGTSS’ (B). The X-axis represents the ranking and the Y-axis represents Cumulative probability. The more surface under the cumulative ranking indicates the more benefit of the intervention. Small-study effects assessed via comparison-adjusted network funnel plots for the outcome ‘Y-BOCS’ (C) and ‘YGTSS’ (D).

Figure 7. Network meta-regression coefficients based on age, sex and three therapy for the outcome ‘Y-BOCS’ (A–C) and ‘YGTSS’ (D–F). DBS, deep brain stimulation, rTMS, repeat transcranial magnetic stimulation.
patients, such as comorbidities, tic severity, and drug tolerance, was high. Therapy must be individualized and the choice of treatment method depends on the patient's condition [36]. Our result shows that in terms of the improvement of tic symptoms, DBS is the best. As in clinical practice, DBS is the last choice for the treatment of refractory patient. We did not analyze the efficacy of different DBS targets; however, we notice that the thalamus exhibits a most significant improving in the YGTTSS score [37]. In the future, more detailed compare between different DBS target should be conducted. Our results also showed that the effect of BT was similar to DBS in improving tic symptoms. The efficacy of BT has been proved in many trails. There exists some major barrier to wider implementation of BT is few trained therapists, and high cost, long course. Based on this barrier, the videoconference delivery BT has been applied, and some RCT trails shows that videoconference delivery BT has equal efficacy to face to face treatment. Therefore, our result provides a direction for the treatment of tic symptom. In addition, OCD is one of the most common comorbidities of TS, which affects the quality of life and tolerance to treatment [38]. Our result demonstrated that rTMS is most effective in improving the obsessional symptoms, which is consistent with a previous study showing that rTMS is more effective in treating TS patients who have a comorbidity like OCD [39]. This result provides a direction for the selection of treatment regimens in these patients. When choosing a therapeutic strategy for TS, the severity of tic symptoms and comorbidities should be considered. The choice of treatment depends on the patient’s specific situation.

Limitations: First, the target and parameter of DBS and rTMS were not under consideration. Secondly, the adverse effect of therapies was quite different. We described the adverse effect of therapy methods. However, we did not analyze the adverse reactions because of the lack of a quantitative index. Finally, our results, while borne out by rigorous statistical analyses, may not capture the full complexity of variable individual responses to one treatment or another - or one target or another - and that further head-to-head studies are needed to further elucidate optimal therapeutic approaches.

Conclusion: Our results showed that BT, DBS, and rTMS are effective in treating TS. DBS is more effective in improving the tic symptoms, and rTMS is more effective in improving the obsessional symptoms.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest’s statement

The authors declare no conflict of interest.

Additional information

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