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A Systematic Review of the Safety and Tolerability of Theta Burst Stimulation in Children and Adolescents

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Abstract

Objectives: Theta burst stimulation (TBS) is often used in clinical practice and research protocols for adults with neuropsychiatric disorders. There are substantial knowledge gaps related to the application of TBS in children and adolescents. This systematic review examined the safety and tolerability of TBS in children and adolescents.

Materials and Methods: A systematic review of human TBS studies in children and adolescents was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The following inclusion criteria were applied: 1) articles in English language only; 2) studies that included child and adolescent participants (up to 21 years of age); 3) studies that administered intermittent TBS or continuous TBS or both to participants; 4) studies that had an outcome measure; and 5) availability of full text material. The primary outcome measures were tolerability and safety. When feasible, the clinical effects were reviewed.

Results: Twenty relevant articles met the criteria for inclusion. The reported adverse events were mild and similar to what is noted in adult studies. The most common symptom was headache. One case report described a seizure induced by TBS. Collectively, the studies were heterogeneous but the methodologic quality of randomized trials was high.

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Authorship Statement

Rana Elmaghraby, Qi Sun, Can Ozger, Julia Shekunov, Magdalena Romanowicz, and Paul Croarkin conceptualized the review and search. Rana Elmaghraby, Qi Sun, and Paul Croarkin screened the articles. Rana Elmaghraby and Qi Sun extracted the data from articles. All authors contributed to drafts of the manuscript and approved the final version of the manuscript.

Conclusions: TBS interventions in children may have similar safety, tolerability, and feasibility as compared to adults. However, long-term, follow-up studies of TBS are lacking. Future dose-ranging studies with systematic assessment of adverse events will be important in the translation of findings with TBS from adults to youth.

Keywords

Adolescents; children; systematic review; theta burst stimulation; transcranial magnetic stimulation

INTRODUCTION

Theta burst stimulation (TBS) is a patterned form of transcranial magnetic stimulation (TMS) that delivers brief high-frequency pulses of stimulation to alter cortical function. Research with TBS was first introduced in 2005 and suggested that this form of stimulation produces more rapid changes in synaptic plasticity compared to standard low- and high-frequency stimulation (1). TBS is purported to mimic the natural rhythm of neuronal activity in the brain (1,2). In TBS dosing typically, 3 pulse, 50 Hz bursts are delivered at 5 Hz which is every 200 msec (1,3). However, there are variations in published TBS protocols. For example, 30 Hz bursts are used in some studies. Ongoing research has demonstrated that TBS has utility in neurophysiological and interventional studies (4). In 2018 the FDA cleared intermittent theta burst stimulation (iTBS) delivered to the left dorsolateral prefrontal cortex for the treatment of major depressive disorder (MDD) in adults (3).

Continuous TBS (cTBS) and iTBS are two forms of TBS that are most commonly used in studies. In general, iTBS is thought to induce cortical excitability or changes in long-term potentiation while cTBS has inhibitory effects and enhances long-term depression (5–7). However, these characterizations of cTBS as inhibitory and iTBS as excitatory have been increasingly called into question as there may be substantial individual variability (8). The efficacy of TBS has been studied in adults with a variety of neurologic and psychiatric conditions. There are limited data and systematic review articles regarding the use of theta burst in children and adolescents (4).

Conceptually, TBS may have advantages compared to standard TMS protocols in children and adolescents. Treatment protocols with TBS may have greater tolerability with lower stimulation intensities. Sessions of TBS are typically delivered over the course of 12 min or less as compared to 30–40 min in standard TMS protocols (4,9). TBS may produce more lasting therapeutic changes in the early stages of neuropsychiatric disease (4,9). However, the potential limitations, tolerability, and adverse effects in developing children are not fully understood (9,10). A recent, international expert consensus guideline provided safety recommendations for TMS protocols. However, this guideline did not specifically address the application of TBS in children and adolescents (11). Systematic study of TBS is important as it is now commonly considered and used in children and adolescents outside of research protocols (9,12). This systematic review aimed to examine existing studies regarding the safety and tolerability of TBS in children and adolescents. When available, clinical effects were reviewed. Studies of interest included participants who were 21 years

of age and younger, consistent with relevant FDA guidance operationalizing the definition of adolescence (13).

MATERIALS AND METHODS

A systematic review of the literature on TBS protocols in children and adolescents was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (14).

Data Sources and Search Strategies

A comprehensive search of several databases from inception to December 31, 2020, limited to the English language, was conducted. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus.

The search strategy was designed and conducted by a medical librarian with input from the authors (R.E., Q.S., C.O., J.S., M.R., and P.E.C.). Controlled vocabulary supplemented with keywords was used to search for studies describing the use and safety of TBS. The search strategy is included in Appendix A.

Study Selection

The following inclusion criteria were applied: 1) articles in the English language; 2) studies that include children and adolescents among their participants, up to 21 years of age; 3) studies that administer iTBS or cTBS or both; 4) studies that had safety, tolerability, or clinical outcome data; and 5) availability of full text material. Preclinical studies, ongoing clinical trials, and review articles were excluded but the respective references were reviewed for additional potential studies.

Data Extraction and Analysis

Two authors (R.E. and S.Q.) independently assessed each title and abstract for inclusion based on eligibility criteria. The authors then reviewed full-text papers and extracted the following data: study designs, demographics of participants, TBS protocol/procedure/parameters, and outcome measures including safety and tolerability of TBS. The extracted data were summarized and included in a table that was reviewed independently by each investigator. A third author (P.E.C.) reviewed, discussed, and resolved any discrepancies from data extraction. As the studies of interest had small sample sizes in some cases, age ranges outside of the age of interest, and heterogeneous methodology, it was not appropriate to conduct a meta-analysis. The authors compiled a descriptive synthesis of available findings.

RESULTS

Overview

The initial search identified 3244 articles and 20 met eligibility criteria. The PRISMA diagram is shown in Figure 1 (14). The studies are summarized in Table 1. There were 5 randomized controlled trials, 13 observational or open-label studies, 1 case series, and 1 case report.

Adverse Events

In general, the reported adverse events were mild and similar to what is noted in adult studies. One case report described a seizure induced by iTBS (32). One case series described treatment emergent manic symptoms induced by iTBS (31). Commonly reported adverse events included: headache (6.6–16.7%), dry eyes (16.7% in one study), abdominal pain (16.7% in one study) fatigue (10% in one study), dizziness (9% in one study), and nausea (5–7%).

Tolerability

Child and adolescent participants tolerated TBS. Most participants who had discomfort were able to tolerate the full treatment series and did not require medications to treat the discomfort.

Randomized Trials

Wu and colleagues reported on a sham-controlled trial for 30 Hz cTBS in participants (N = 12) with chronic tic disorders based on Diagnostic and Statistical Manual-IV-TR (DSM-IV-TR) criteria (15,33). One ten-year-old participant had a high motor threshold (MT) and as a result did not receive cTBS. Otherwise, six participants received active cTBS and six received sham cTBS both applied to the supplementary motor area. In the group receiving active cTBS there was a 12-year-old participant, two 10-year-old participants, a 13-year-old participant, and a 16-year-old participant. Active cTBS consisted of 5 Hz/30 Hz delivered at 90% resting MT. Four trains of cTBS were administered daily for two days. The first and second trains of cTBS were spaced 15 min apart. The third train of cTBS was 60 min after the first train and the fourth train of cTBS was 75 min after the first train of cTBS. All (N = 12) participants who received active or sham cTBS completed the study. Three patients receiving active cTBS reported mild adverse events (abdominal pain, headache, and dry eyes) (15).

Ni and colleagues reported on a randomized, sham-controlled, cross-over trial of iTBS delivered to 25 participants with autism spectrum disorder (ASD) with a mean age of 20.8 years (16). The Autism Diagnostic Interview-Revised (34) and Autism Diagnostic Observation Schedule (ADOS) (35) were used to confirm an ASD diagnosis. The participants received iTBS over the bilateral DLPFC, bilateral posterior superior temporal sulcus, and inion (the sham control stimulation). The iTBS was delivered in trains that consisted of three pulses delivered at 50 Hz given ten times every 200 msec. The TBS train was delivered 20 times every 10 sec for a total of 600 pulses. For the stimulus intensity, the pulse was set at 80% active MT for participants and at 60% active MT for the sham group.

Three participants felt transient discomfort because of muscle twitches around the eyes. No other significant adverse events were reported and all participants tolerated iTBS (16).

Blumberger and colleagues reported on a randomized, multicenter, non-inferiority clinical trial with 414 participants between the age 18–65 receiving either rTMS or iTBS (3). The average age of participants in the iTBS arm was 42 years and the breakdown of patients aged 18–21 years was not available. The participants were diagnosed with a current treatment-resistant major depressive episode or could not tolerate at least two antidepressants in the current episode. The diagnosis of MDD was based on an interview with the Mini-International Neuropsychiatric Interview (36). Participants were treated with 10 Hz rTMS or iTBS to the left dorsolateral prefrontal cortex, administered five days a week for four to six weeks. Two hundred and eight participants received iTBS. One hundred and thirty-six (65%) participants experienced headaches, 18 (9%) experienced dizziness, 16 (8%) experienced fatigued and 14 (7%) experienced nausea. Although this study demonstrated that iTBS was non-inferior to standard TMS for participants with a treatment-resistant major depressive episode, it is difficult to make any conclusions regarding the participants who were 18–21 years of age (3).

Zhao and colleagues reported on a randomized single-blind pilot study of iTBS and cTBS in 83 abstinent male participants with methamphetamine use disorder who were recruited from a long-term residential treatment facility (17). The diagnosis of methamphetamine use disorder was based on DSM-V criteria (37). The 83 participants were randomly assigned to iTBS over left dorsolateral prefrontal cortex (DLPFC) (active group), cTBS over left DLPFC (active control group), or cTBS over right DLPFC (active group). TBS was administered twice daily for five days for a total of ten TBS sessions. The procedure used for iTBS composed of three pulses of 50 Hz at 70% resting motor threshold (RMT), which was repeated at 5 Hz for 3 min for a total of 600 pulses. cTBS was delivered as three pulse trains of 50 Hz at 70% RMT and was repeated at 200 msec for 40 sec for a total of 600 pulses. All participants tolerated cTBS and iTBS without any significant adverse events. There were no seizures reported. Further analysis of the adverse events indicated that participants in the cTBS left DLPFC group exhibited the lowest percentage of adverse effects and that participants in the cTBS right DLPFC and iTBS left DLPFC demonstrated mild adverse effects (17).

Ni and colleagues completed a four-week randomized, single-blind (participants and caregivers), controlled trial with four-week open-label extension for participants with ASD (18). The ASD diagnosis was based on an interview with the ADOS. The 78 participants (aged 8–17 years) were randomized to active (80% MT) or sham stimulation (60% MT but delivered with the coil tilted 90° from the scalp) of 1200 pulses of iTBS delivered to the posterior superior temporal sulcus of the right and left hemisphere (2400 pulses total) two times per week for four weeks. Participants in both arms were then unblinded and offered eight active sessions for another four weeks (two sessions per week). No seizures were reported. The treatments were generally well-tolerated as 75 participants completed both four-week phases. Side effects (all with an incidence of less than 5%) included scalp pain, headache, dizziness, tinnitus, and anxiety. At four weeks there were no differences between active and sham treatments with respect to clinical effects. However, participants

that received eight weeks of iTBS (four weeks blinded followed by four weeks open-label) demonstrated significant improvements in the social responsiveness scale (38) and the repetitive behavior subscale revised (18,39).

Observational and Open-Label Studies

Wu and colleagues reported on a single session study of TBS in forty participants (N = 16 with Tourette syndrome and N = 24 healthy controls) under 18 years of age (20). The diagnosis of Tourette syndrome was based on DSM-IV-TR criteria. In this study, 31 participants received 32 sessions of TBS at 80% active MT. Young children (<12 years of age) often had higher MTs with stimulation intensities that exceeded the device's capabilities and were not possible to deliver. In these cases, the study team delivered two sessions of TBS at 55% and 70% active MT. The team also changed the TBS burst delivery to 30 Hz to extend stimulation intensity capability. Subsequently, seven participants received nine sessions of 30 Hz TBS at an intensity of 90% resting MT. Three of the 40 participants also received cTBS. One participant received iTBS and cTBS on the same day (sessions two hours apart). There were no serious adverse events related to TBS. Three participants reported a mild headache, one participant noted mild neck stiffness, and one participant noted a mild feeling of a finger twitch which could not be visualized and resolved within 12 hours with no intervention (19).

A later follow-up study by Wu and colleagues examined the effects of a single iTBS session on motor-evoked potential amplitudes in a sample of participants aged 18–42 years (N = 10 with Tourette syndrome and N = 11 healthy controls) (20). The diagnosis of Tourette syndrome was based on DSM-IV-TR criteria. The participants received one session of iTBS delivered to the left motor cortex. There were no reported serious adverse events or adverse events in this study (20).

Oberman and colleagues reported on a study of ASD with male participants, aged 9–18 years (N = 19) who underwent a 40-sec train of 5 Hz/50 Hz cTBS at 80% active MT, delivered to the left motor cortex (21). The cTBS protocol was tolerated with no serious adverse events. Adverse events included a mild headache that was relieved with one dose of acetaminophen. Two other participants noted mild fatigue that resolved the next day (21).

A study by Pedapati and colleagues examined an iTBS protocol in healthy children (based on a clinical interview), aged 10–16 years (N = 14) who received 300 pulses of 5 Hz/30 Hz iTBS at 70% resting MT (22). The authors related that no adverse events were reported spontaneously or with structured interviews. There were no seizures (22).

Hong and colleagues sought to compare the safety and tolerability of TBS protocols with single and paired-pulse TMS protocols (5). The authors retrospectively examined data from (N = 165) participants 6–18 years of age, from various protocols in 2009 through 2014. Diagnoses were made based on clinical interviews. The studies collected adverse event data with a structured questionnaire. The TBS protocols delivered intensities ranging from 60% to 90% of resting MT and 30–50 Hz pulse frequencies delivered in 5 Hz bursts. The total number of pulses in TBS protocols was either 300 or 600. Nine of the participants received both cTBS and iTBS stimulation. Seventysix participants were exposed to TBS protocols

and 89 underwent single or paired-pulse TMS. There was no statistical difference among these two groups with respect to adverse events. Common specific adverse events with TBS included headache (6.6%), arm/hand/other pain (2.6%), numbness or tingling (2.6%), other sensations (2.6%), weakness (1.3%), and other (1.3%) (5).

Pedapati and colleagues examined the neurophysiological effects and tolerability of iTBS in youth with ASD, 13–18 years of age ($N = 9$) and healthy control participants 11–18 years of age ($N = 9$) (23). The ASD diagnosis was based on an interview with the ADOS. Participants received 300 pulses of 5 Hz/30 Hz iTBS at 70% resting MT delivered to the left motor cortex. Adverse event monitoring included a structured interview. One participant noted a mild headache after the iTBS session that resolved with no intervention. Otherwise, iTBS was tolerable to all participants. There were no seizures or serious adverse events (23).

Oberman and colleagues also examined a cTBS protocol in a study plasticity and metaplasticity in patients with ASD and fragile X syndrome (24). The ASD diagnosis was based on an interview with the ADOS. Participants with ASD ($N = 10$, 16–62 years of age), fragile X syndrome ($N = 6$, 16–33 years of age), and healthy controls ($N = 12$, 19–61 years of age) underwent two sessions of cTBS on two consecutive days. During the protocol, 600 pulses of 5 Hz/50 Hz cTBS at 80% active MT applied to the left motor cortex. The cTBS was well tolerated and no adverse or serious adverse events were reported (24).

Dileone and colleagues reported on a study that examined the neurophysiological effects of iTBS on patients with Costello syndrome (molecular diagnosis) and healthy controls (25). The experimental protocol delivered 600 pulses of 5 Hz/50 Hz iTBS at 80% active MT to the right motor cortex. The samples included participants ($N = 4$) aged 17, 18, 19, and 27 with Costello Syndrome and 21 control participants ranging 16–34 years old. There were no adverse or serious adverse events in the study (25).

Abujadi and colleagues presented findings from an interventional study that enrolled male participants aged 9–17 ($N = 10$) with ASD for an open-label trial of iTBS (26). The ASD diagnosis was based on DSM-IV-TR criteria. Participants received 15 sessions with 900 pulses per session of 5 Hz/50 Hz iTBS at 100% active MT delivered to the RDLPFC. The iTBS was tolerated by all participants. All participants completed the study. There were no adverse events, seizures, or serious adverse events (26).

Johkura and colleagues reported on a study of iTBS in 6 participants with chronic post lateral medullary infarction dizziness (clinical diagnosis) and 11 healthy participants with a minimum age of 20 years old (27). The iTBS was applied as 5 Hz stimulation applied for 2 sec for every 10 delivered for a total of 600 pulses at an intensity of 80% of the resting motor potential. iTBS was applied to the cerebellum once a day every day for five consecutive days. All participants tolerated iTBS without significant adverse events. No complications, such as seizures, occurred in any of the participants. One participant reported uncomfortable muscle contraction association with the magnetic stimulation but no muscle damage or reduced muscle function was noted (27).

McNeill and colleagues reported on a counterbalanced, withinparticipants design on 20 participants whose regular alcohol use exceeds recommended weekly guidelines (based on

self-report) with ages between 18 and 27 years old (28). cTBS was delivered to the rDLPFC with a control stimulation of the same intensity of cTBS at the vertex. Participants were randomized to receive cTBS or its control stimulation at the first session and then completed the opposite stimulation in the second session, which was at least one week later. Three pulse bursts at 50 Hz repeated every 200 msec for 40 sec were delivered at an intensity of 80% resting motor potential, resulting in a total of 600 pulses. All participants tolerated cTBS with no reported significant side effects (28).

Dhami and colleagues recently completed a therapeutic trial of TBS with one of the most aggressive protocols to date (29). This study enrolled 20 youth (ages 16–24) with MDD based on an evaluation with the Mini-International Neuropsychiatric Interview. The participants received ten sessions of sequential, bilateral 5 Hz/50 Hz TBS. Each session included 1800 pulses of cTBS delivered to the RDLPFC followed by 1800 pulses of iTBS delivered to the LDLPFC prefrontal cortex alternately. All TBS sessions were delivered at 80% active MT. The order of iTBS and cTBS was randomized for each patient. Participants endorsed mild headaches and other mild adverse events. There were no seizures or serious adverse events. There was a statistically significant reduction in depressive symptom severity based on ratings with the 17-item Hamilton Rating Scale for Depression (29, 40).

Jannati and colleagues reported on a study of cTBS in 11 participants with ASD (diagnosed with the ADOS) and 18 healthy controls between the ages of 10 and 16 (30). The TBS was delivered in a manner consistent with standard protocols. cTBS was applied as 200 bursts of three pulses at 50 Hz, repeated at 200-msec intervals for 40 sec (for a total of 600 pulses). cTBS were applied to the left motor cortex at 120% of individual RMT and 80% of active MT. All participants tolerated cTBS without any significant adverse event. One participant experienced mild scalp irritation that resolved quickly without medication (30).

Case Series

Shere and colleagues report on three participants with depression (based on DSM-IV-TR) who received bilateral TBS protocol (31). The TBS protocol was delivered at 1800 intermittent pulses with a 2-sec stimulation interval and an 8-sec inter-train interval over the left DLPFC followed by 1800 continuous pulses over the right DLPFC. Both iTBS and cTBS were delivered at 80% resting motor potential. After 3–6 sessions of TBS, two 17-year-olds developed symptoms of mania. There were no other significant adverse effects reports in these three cases and all three participants tolerated the treatment (31).

Case Reports

In 2018, Purushotham and colleagues published a case report describing a seizure in a teenager during iTBS (32). A 15-year-old female patient with schizophrenia (diagnosed with a clinical interview) was enrolled in a neurophysiological study arm meant to deliver 600 pulses of iTBS at 80% active MT. Notably, the participant had no prior or current treatment with psychotropic medications. Prior to iTBS a physical examination, electrocardiogram, electrolytes, complete blood count, liver function tests, renal function tests, thyroid function tests, and computed tomography of the brain were all normal. There was no personal history of head injury, seizures, or other neurological disorders. The family psychiatric

and neurological history was normal. The authors described a seizure with limb muscle contractions, eyelid fluttering, jaw contraction, foamy saliva, and urinary incontinence. The participant regained consciousness after 1 min but was disoriented for approximately 20 min. The authors highlighted that this was the first published seizure with TBS in a child or adolescent (32).

Study Quality Assessments

The authors evaluated the five randomized controlled trials with the Newcastle-Ottawa Quality Assessment Scale (Table 2) (41). The scale for randomized controlled trials assesses selection (four items: case definition, case representativeness, control selection, control definition), comparability (one item), and exposure (three items: ascertainment of exposure, method of ascertainment for cases and controls, and nonresponse rate). Each item is awarded a maximum of one star with the exception of the comparability item which can be given a maximum of two stars. A greater number of stars denotes higher quality methodology. The observational studies, case series, and case report were not assessed for quality. The five clinical trials reviewed were high quality. Otherwise, currently available literature focused on the use of TBS in children and adolescents is difficult to assess, interpret, and synthesize. The study designs and samples were heterogeneous. Studies often included a wide age range encompassing adults, adolescents, and children. The majority of the manuscripts had observational or open-label study designs.

DISCUSSION

Clinical and research protocols increasingly use TBS dosing for neuropsychiatric disorders such as depressive disorders and ASD (4). At present, FDA-labeled indications include iTBS for the treatment of MDD in adults (3). Despite considerable knowledge gaps, children and adolescents are increasingly exposed to TBS in the course of research protocols or off-label use in clinical practice (4,9,12). Brain stimulation research in children and adolescents is underdeveloped and this is particularly evident with respect to TBS protocols (8,9,42). Herein, we sought to systematically review existing literature to examine the safety and tolerability of TBS in youth.

The available published information is encouraging with respect to the safety and tolerability of TMS in children and adolescents. The identified frequency of adverse events is similar to what is noted in adult studies. Available information suggests that TBS and standard TMS protocols have similar side effects and tolerability in children and adolescents. Future studies should collect systematic data on adverse events with rating scales and consider long-term (6–12 months) follow-up assessments to examine adverse events, hearing, and neurocognitive assessments. Dose-ranging studies in youth (with respect to stimulation intensity, pulses per session, and total number of sessions) for tolerability and clinical effects should be conducted in the future. Prior commentaries have emphasized the perils of rapid adoption of adult brain stimulation protocols for children and adolescents in the context of divergent anatomy and neurophysiology (9,10,12). Historical neuropharmacology studies serve as a reminder of the challenges in translating adult findings to children and adolescents (9).

Accelerated protocols with TBS are an emerging area of interest for therapeutic studies (43,44). Accelerated protocols apply more than one session of TBS daily. Accelerated TBS studies with adults have become gradually more aggressive (with respect to number of daily sessions) over time. Recent systematic reviews and available studies suggest that accelerated TBS protocols are feasible, safe, and tolerable in adults. Notably, Wu and colleagues conducted an accelerated cTBS protocol in youth which was well tolerated with no serious adverse events.

The existing publications describing randomized controlled trials of TBS in children and adolescents are high quality. Other studies of TBS in children and adolescents have heterogeneous methodology and quality. Many studies had small sample sizes and flexible protocols making the interpretation of findings difficult. Some studies included wide age ranges (children, adolescents, and adults). Many studies were cross-sectional. Sham stimulation or control groups were not used consistently. Hence, the interpretation of adverse events and clinical effects is challenging (9).

Future studies with larger sample sizes are needed to continue to determine whether there is an important role for TBS in children and adolescents. Forthcoming studies should use structured rating instruments for side effects. Sham conditions and blinding should also be considered carefully in future work (9,13,45). Although there have been no major adverse effects noted, long-term follow-up studies of children and adolescents completing TBS protocols would be informative. Unfortunately, relevant regulatory incentives and resources are somewhat limited (13). Future efforts in this area will require considerable ingenuity and unique collaborations (9).

In summary, limited prior work suggests that TBS interventions have similar safety, tolerability, and feasibility, in children and adolescents as compared to adults. Caution is warranted in interpreting available data. There are many opportunities for enhancing the methodologic quality of future studies of TBS in youth.

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Conflict of Interest:

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APPENDIX

SEARCH STRATEGY

Database(s): Ovid MEDLINE(R) 1946 to December 2020 and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) Daily, EBM Reviews—

Cochrane Central Register of Controlled Trials December 2020, EBM Reviews—Cochrane Database of Systematic Reviews 2005 to December 2020, Embase 1974 to December 2020.

1	Transcranial Magnetic Stimulation/
2	“transcranial magnetic stimulation”.mp.
3	1 or 2
4	Theta Rhythm/
5	(theta* adj1 (burst* or rhythm*)).mp.
6	4 or 5
7	3 and 6
8	“theta burst stimulation”.mp.
9	7 or 8
10	limit 9 to english language [Limit not valid in CDSR; records were retained]
11	limit 9 to no language specified [Limit not valid in CDSR; records were retained]
12	10 or 11
13	remove duplicates from 12

SCOPUS

1	TITLE-ABS-KEY (“transcranial magnetic stimulation”)
2	TITLE-ABS-KEY ((theta* W/1 (burst* OR rhythm*)))
3	1 and 2
4	TITLE (“theta burst stimulation”)
5	3 or 4
6	INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)
7	5 not 6
8	DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh) OR DOCTYPE(ch)
9	7 not 8
10	LANGUAGE(english)
11	9 and 10

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COMMENTS

A helpful narrative summary of studies of theta burst stimulation in children and youth, focusing on adverse events reported, which are primarily at most mild.

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Elamghraby et al. have provided a timely and comprehensive summary of the safety and tolerability of theta burst stimulation (TBS) in youth. The body of work in this field remains small, thus they have appropriately emphasized qualitative aspects of each study. The increasing interest in using TBS in the pediatric clinical population should drive significant interest to this work which will be useful in designing monitoring protocols and capturing potential risks.

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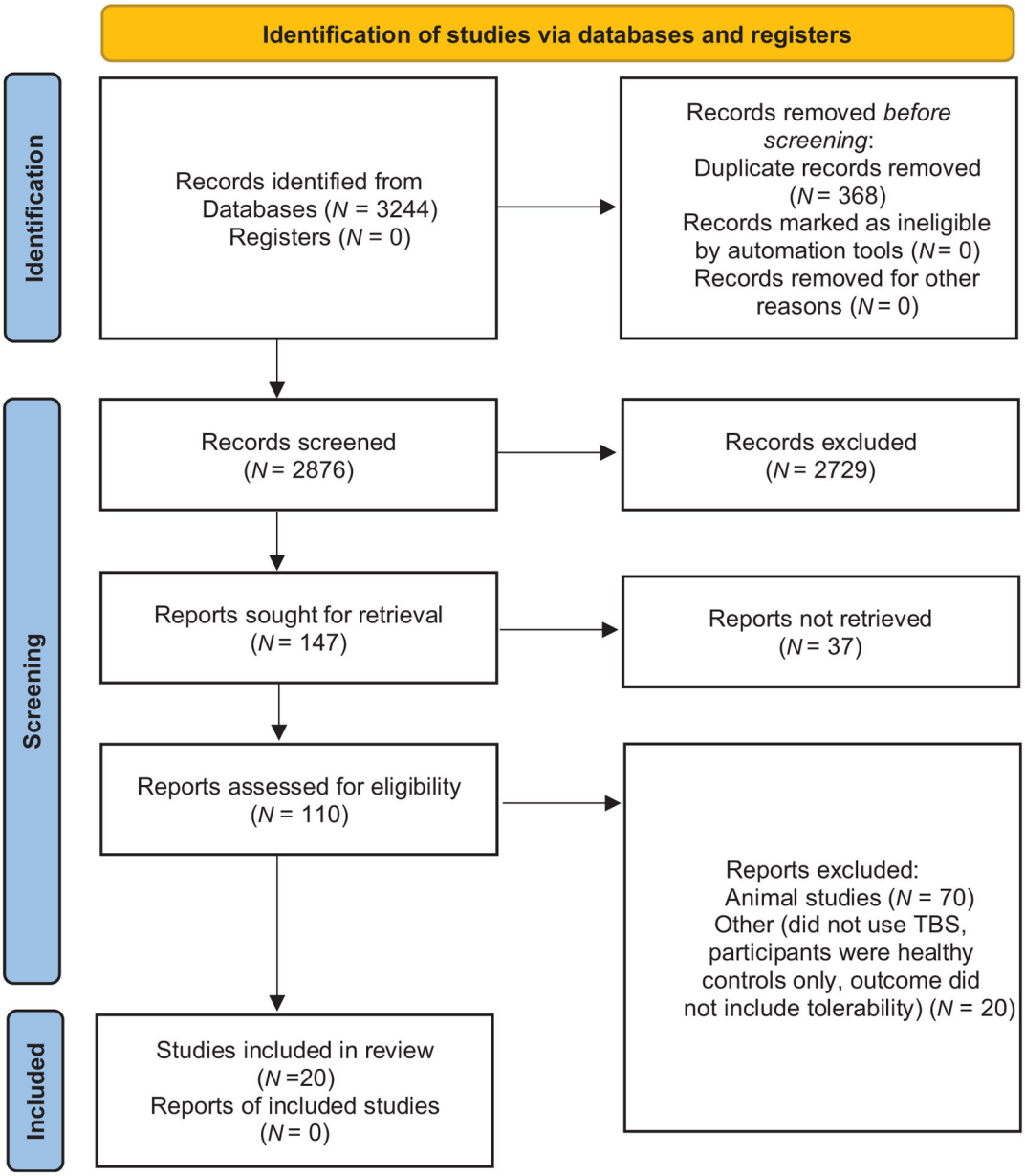

Figure 1.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. TBS, theta burst stimulation.

Table 1.

Summary of Previous TBS Studies in Children and Adolescents.

Study	Age and *N*	Stimulation intensity	Number of sessions per day	Total number of sessions	Adverse events
	Randomized trials				
Wu et al. (15)	10–22 years (*N* = 12)	90% resting MT	4	8	Mild abdominal pain: 16.7% Mild headache: 16.7% Mild dry eyes: 16.7%
Ni et al. (16)	Older than 18 years (*N* = 25)	80% active MT 60% active MT-Sham group	1	1	Muscle twitches around the eye resulting in mild discomfort: 12% No serious adverse events No seizures
Blumberger et al. (3)	18–65 years (*N* = 414)	120% resting MT	1	20–30	Headaches: 65% Dizziness: 9% Fatigue: 8% Nausea: 7% No serious adverse events No seizures
Zhao et al. (17)	18–60 years (*N* = 83)	70% resting MT	2	10	Headache Scalp pain Neck pain Burning sensation Sleepiness Trouble concentrating Tingling Itching Total adverse events: 5.5% in the cTBS left DLPFC group and mild to moderate in the iTBS left DLPFC and cTBS on right DLPFC group (this article did not specify rates of specific adverse events) No serious adverse events No seizure
Ni et al. (18)	8–17 years (*N* = 78)	80% active MT	1	8 for phase 1 and 8 for phase 2	Local pain (10% in active and 29% in sham) Headache, dizziness, tinnitus, and anxiety (less than 5%) No serious adverse events No seizure
	Observational and open-label studies				
Wu et al. (19)	8–17 years (*N* = 40)	80% active MT	1	1	Mild headache: 7.0% Neck stiffness: 2.3% Sensation offinger twitching: 2.3%
Wu & Gilbert (20)	18–42 years (*N* = 21)	80% active MT	1	1	None reported
Oberman et al. (21)	9–18 years (*N* = 19)	80% active MT	1	1	Mild headache: 5.3% Fatigue: 10.5%
Pedapati et al. (22)	10–16 years (*N* = 14)	70% resting MT	1	1	None

Study	Age and *N*	Stimulation intensity	Number of sessions per day	Total number of sessions	Adverse events
Hong et al. (5)	6–18 years (*N* = 76)	60–90% resting MT	1	1	Mild headache: 6.6% Moderate arm/hand/other pain: 2.6% Numbness/tingling: 2.6% Other sensations: 2.6% Weakness: 1.3% Other: 1.3%
Pedapati et al. (23)	11–18 years (*N* = 18)	70% resting MT	1	1	Mild headache: 5.6%
Oberman et al. (24)	16–62 years (*N* = 28)	80% active MT	1	2	None
Dileone et al. (25)	16–34 years (*N* = 25)	80% active MT	1	1	None
Abujadi et al. (26)	9–17 years (*N* = 10)	100% active MT	1	15	None
Johkura et al. (27)	Minimum age 20 years old (*N* = 6)	80% resting MT	1	5	Uncomfortable muscle contraction: 1 participant No serious adverse events No seizures
McNeill et al. (28)	18–27 years (*N* = 20)	80% resting MT	1	1	None
Dhami et al. (29)	16–24 years (*N* = 20)	80% resting MT	1	10	Mild headache: 65% Mild chest tightness: 5% Mild scalp pain: 5% Mild nausea: 5% Mild gastrointestinal symptoms: 5% Mild nasopharyngitis: 5% Mild restlessness Mild discomfort No serious adverse events No seizures
Jannati et al. (30)	10–16 years (*N* = 29)	120% resting MT 80% active MT	1		Mild scalp irritation: 3.4% No serious adverse events No seizures
	Case series				
Shere et al. (31)	17–21 years (*N* = 3)	80% resting MT	1	3–6	No serious adverse events No seizures
	Case reports				
Purushotham et al. (32)	15 years (*N* = 1)	80% active MT	1	1	Seizure

cTBS, continuous theta burst stimulation; DLPFC, dorsolateral prefrontal cortex; iTBS, intermittent theta burst stimulation; MT, motor threshold; TBS, theta burst stimulation.

Table 2.

Quality Assessment of Randomized Trials With Newcastle-Ottawa Scale.

Study reference	Selection	Comparability	Exposure
	Randomized trials		
Wu et al. (15)	**	**	***
Ni et al. (16)	****	**	***
Blumberger et al. (3)	****	**	***
Zhao et al. (17)	****	**	***
Ni et al. (18)	****	**	***

Ratings are based on selection of subjects (four possible stars evaluating definition, representativeness, selection of controls, and definition of controls), comparability (two possible stars evaluating use of controls), and exposure (three possible stars evaluating ascertainment of exposure of TBS and response rate).