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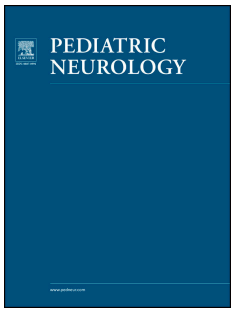

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Safety of Transcranial Magnetic Stimulation in Children: A Systematic Review of the Literature

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Abbreviations:
TMS - Transcranial magnetic stimulation
TBS - Theta-burst stimulation
ADHD - Attention-deficit/hyperactivity disorder
MEP - Motor evoked potentials
SICI - Short intracortical inhibition
GABA – Gamma-aminobutyric acid
MEG – Magnetoencephalography
EEG – Electroencephalography
CNS – Central Nervous System

Key words: transcranial, neurostimulation, pediatric, adverse, seizure

Contributors' Statements:

Corey Allen carried out the literature search and the analyses, wrote and revised the manuscript and approved the final manuscript as submitted.

Benzi Kluger conceptualized the study, critically reviewed the manuscript and approved the final manuscript as submitted.

Isabelle Buard supervised literature search, analyses and writing process, reviewed and revised the manuscript and approved the final manuscript as submitted.

ABSTRACT

Context: Data and best practice recommendations for transcranial magnetic stimulation (TMS) use in adults is largely available. While there is less data in pediatric populations and no published guidelines, its practice in children continues to grow.

Methods: We performed a literature search through PubMed to review all TMS studies from 1985-2016 involving children and documented any adverse events. Crude risks were calculated per session.

Results: Following data screening, we identified 42 single pulse (spTMS) and/or paired pulse (ppTMS) TMS studies involving 639 healthy children (HC), 482 children with CNS disorders, and 84 epileptic children (EP). Adverse events (AEs) occurred at rates of 3.42%, 5.97%, and 4.55% respective to population and number of sessions. We also report 23 repetitive TMS (rTMS) studies involving 230 CNS and 24 EP with AE rates of 3.78% and 0.0% respectively. We finally identified three theta-burst stimulation (TBS) studies involving 90 HC, 40 CNS and no EP, with AE rates of 9.78% and 10.11% respectively. Three seizures were found to have occurred in CNS individuals during rTMS, with a risk of 0.14% per session. There was no significant difference in frequency of AEs by group (p = .988) nor modality (p = .928).

Conclusions: Available data suggests that risk from TMS/TBS in children is similar to adults. We recommend that TMS users in this population follow the most recent adult safety guidelines until sufficient data are available for pediatric specific guidelines. We also encourage continued surveillance through surveys and assessments on a session-basis.

INTRODUCTION

Transcranial magnetic stimulation (TMS) is a noninvasive technique for cortical stimulation that uses electromagnetic induction to generate a strong fluctuating magnetic field which induces intracranial currents[1]. Single pulse (spTMS) and paired-pulse TMS (ppTMS) studies have been shown to be safe and effective in studying a variety of measures of motor cortex excitability including resting motor threshold, motor evoked potential amplitude, recruitment curves, cortical silent period, short interval intracortical inhibition, long interval intracortical inhibition and intracranial facilitation[2]. It is now a state of the art technique for studying neurophysiology in vivo. Repetitive TMS (rTMS) applies repeated TMS pulses at set frequencies or bursts of stimulation to induce changes in cortical excitability which last longer than the period of stimulus administration by minutes to hours with more durable changes in clinical outcomes reported when rTMS is given in daily sessions for 1-6 weeks[3]. These alterations have generally been observed as a decrease in cortical excitability with low-frequency stimulation (≤ 1 Hz) and an increase in cortical excitability with high frequency rTMS (≥ 5 Hz)[3]. rTMS demonstrates therapeutic potential for many conditions in adults including depression[4], eating disorders[5], epilepsy[6], schizophrenia[7], tinnitus[8, 9], migraine[10], and Parkinson's Disease[9 11]. In children, possible therapeutic benefits have been reported for motor function and tics[12, 13 14 15]. Theta-burst stimulation (TBS) is a newer form of rTMS that administers 50 Hz bursts of 3 pulses every 200 msec either continuously (cTBS) or in intermittent 2-second trains every 10 seconds (iTBS)[16]. TBS may induce longer lasting cortical inhibition (cTBS) or excitation (iTBS) than standard rTMS[16]. In general, benefits when present have been of small to moderate magnitude and short-lived. Still, given the potential for

clinical benefit and limitations of medical options there is a need for further studies of rTMS/TBS as a therapeutic intervention[4, 8].

The use of TMS in both healthy and clinical adult populations has been associated with several adverse events of varying severity. The most common are transient headaches and scalp discomfort, which are thought to be due to activation of scalp pericranial muscles[17, 18]. However, more severe adverse effects may include mood changes, and induction of seizures[17]. Seizures during TMS are thought to be a result of cortical pyramidal cell activation, spread of excitation to neighboring neurons, and persistent changes in motor cortical inhibition[19]. Whether TMS can induce seizures is theoretically possible but controversial given the extremely rare occurrence. We wanted to provide a brief but complete review of all published studies where TMS have been used in children, and describe adverse events, in order to provide a safety profile of TMS in children for researchers and clinicians as well as safety measures for IRBs. This is of crucial importance regarding the increasing number of published studies using these tools on pediatric populations (Figure 1).

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for the conduct and reporting of this review. The different phases of this systematic review are displayed in the PRISMA flowchart (Figure 2).

Literature Review

An extensive literature search for English language studies on TMS use in children was

conducted through PubMed and links from publications from 1/1/1985 through 10/31/2016. Review articles were excluded except when presenting novel data. The searches used included the following key words: transcranial magnetic stimulation, TMS, TBS, Children, Child, Pediatric. Dealing with missing data: while our searches were comprehensive, there is a possibility that we may have missed relevant studies, however we believe this to be unlikely. We sought missing data from study authors; yet, many failed to respond. We intended to present all studies in the main report (Table 1). All applicable articles were reviewed for patient demographics (gender, age, and patient phenotype), TMS protocol used (TMS modality and stimuli intensity) and adverse events reported.

Grading adverse events

Adverse events were graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE v4.0)[20]. This commonly accepted grading scale divides adverse events into five different categories (Grade 1-5) depending on their severity. Only Grades 1-3 are present in this report. Grade 1 is a mild event that needs no intervention, Grade 2 is a moderate event with noninvasive intervention needed, and Grade 3 is a severe event, but not life-threatening, that calls for hospitalization.

Statistical Analysis

We extracted all adverse events reported in each TMS and/or TBS study. We computed the proportion estimate of crude risk per session, population, and modality. We also

separated single pulse/paired pulse, rTMS and TBS studies and tested for group differences. Risks were calculated as per-session risk. Confidence intervals were calculated utilizing the Clopper-Pearson method in SPSS software version 23, and group differences were calculated via multivariate ANOVA with WLS weighting per session.

RESULTS

Studies including single and paired-pulse TMS

We identified 42 studies utilizing single or paired pulse techniques in child patients[21-62]. This included 639 healthy children, 482 children with central nervous system (CNS) disorders, and separately 84 epileptic children. Of these studies, 10 reported adverse events (Table 2)[21, 23, 33, 37, 39, 40, 43, 48, 58, 63], and 9 were included in our calculations[21, 23, 33, 37, 39, 43, 48, 58, 63]. Adverse events by population were distributed as follows: 25 events in the healthy participants group, 50 events in CNS disorder participants group, and 4 events in the epileptic population. Parents of 4 epileptic children out of total 34 reported a small increase in seizures frequency following TMS, with no episode of status epilepticus[48]. Within 3 days after TMS, parents confirmed that seizures resumed to initial frequency ranging from 3 times per month to continuous. The risk of any adverse event during spTMS or ppTMS in healthy populations is 0.0342 (95% CI: 0.0223 - 0.0501) per session, 0.0597 (95% CI: 0.0447 - 0.0780) per session for patients with a CNS disorder, and 0.0455 (95% CI: 0.0125 - 0.1123) per session for those with epilepsy.

Mild adverse events reported included local discomfort (n=28)[23, 37, 62], headache (n=14)[33, 39, 43], tingling/dullness (n=8)[39, 43, 58], other pain (n=7)[33, 39, 43], scalp pain (n=5)[39, 43], nausea/vomiting (n=4)[33, 39, 43], self-reported increase in seizure frequency for up to

three days following stimulation in epileptic children (n=4)[48], loss of appetite (n=2)[39], hearing change (n=1)[39], and other (n=2)[39, 43]. Moderate adverse events include headache (n=1)[39], ringing of the ears (n=1)[43], and neurocardiogenic syncope (n=2)[21].

Studies including repetitive TMS

We identified 23 rTMS studies involving child patients[13-15, 21, 64-82] including a total of 230 children with CNS disorders and 76 children with Epilepsy. There were 81 adverse events that were attributed to rTMS protocols in the CNS disorder population (Table 2). The mild adverse events were as follows: headache (n=45)[15, 21, 64, 69-71, 75, 78], dizziness (n=8)[66, 69, 70], jaw twitching (n=4)[66], nausea/vomiting (n=4)[21, 75], anxiety (n=3)[69], neck stiffness (n=3)[21], tingling/dullness (n=3)[69, 75], scalp pain (n=2)[13, 67], neck pain (n=2)[70], restlessness (n=1)[77], and sleepiness (n=1)[14]. Moderate adverse events include generalized tonic-clonic seizure (n=3)[65, 68, 72] and rapid moodswings (n=1)[77]. The only severe adverse event to occur in rTMS stimulation is 8-9 hours of stimulation-induced hypomania (n=1)[72]. The risk of any adverse event during rTMS by population is 0.0378 (95% CI: 0.0301 - 0.0468) per session for individuals with CNS disorders, and 0 (95% CI: 0.0000 - 0.0070) per session for patients with epilepsy. Inside this bracket of adverse events, the crude risk of seizure for patients with CNS disorders per session is 0.0014 (95% CI: 0.0003 - 0.0041).

Studies including theta-burst stimulation

We identified three theta-burst studies involving 90 healthy children and 40 children with CNS disorders[43, 62, 79]. Of these studies, two identified adverse events (Table 2)[43, 62]. No

seizures were reported, thus the crude risk of seizures is 0 (95% CI: 0.0000 - 0.0202). Nine adverse events were reported in healthy children, thus the crude risk per session is 0.0978 (95% CI: 0.0457 - 0.1776). In the population with CNS disorders, 9 mild self-limited adverse events were attributed to TBS with a crude risk per session of 0.1011 (95% CI: 0.0473 - 0.1833). The mild adverse events are as follows, and all were resolved without medical intervention: headache (n=8)[43, 62], tingling/dullness (n=2)[43], other sensations (n=2)[43], finger twitching (n=1)[62], weakness (n=1)[43], other pain (n=1)[43], neck stiffness (n=1)[62], and other (n=1)[43]. There was only one moderate adverse event: arm/other pain (n=1)[43].

Comparing Populations and Modalities

Frequency of adverse events was similar for groups ($F(6,150) = .156$, $p = .988$) as well as modalities ($F(6,150) = .316$, $p = .928$). Frequencies per grade of adverse event, per modality, and per population are represented in figure 3. As shown, adverse events deemed Grade 1 (mild) in healthy populations, occurred at rates of 3.42% and 9.78% per session in sp/ppTMS and TBS respectively. In CNS populations, Grade 1 events occurred at rates of 5.62%, 3.55%, and 8.99% per session in sp/ppTMS, rTMS, and TBS respectively. Grade 2 (moderate) events occurred at rates of .36%, .19%, and 1.12% per session in sp/ppTMS, rTMS, and TBS respectively. Grade 3 (severe) events occurred at a rate of .05% in rTMS sessions. For Epileptic populations, Grade 1 adverse events occurred at a rate of 4.55% per session in sp/ppTMS stimulation.

DISCUSSION

This systematic review focused on the use of magnetic currents as tools to investigate plasticity in the developing brain or to explore their therapeutic potential in children with CNS disorders or epilepsy.

While many people have worries regarding the safety of TMS in the child population, our literature review adds to previous ones showing that most adverse events are mild and overall uncommon[83, 84]. However, we did find three reports of new onset seizures[65, 68, 72] that are lacking in similar recent reviews. In two cases, patients were diagnosed and treated for depression with sertraline which has been associated with seizures, albeit rarely[85, 86]. In the first case, prolonged hypomania was also reported. Hypomania is the worst grade level for adverse events in this review. While this is a unique case, hypomania is more likely a side-effect of selective serotonin reuptake inhibitor-type antidepressants such as sertraline[87]. In the second case[65], atypical antipsychotic olanzapine was also taken by the patient on a daily basis. While antipsychotics decrease seizure threshold to varying degrees, olanzapine is known to be safer than other atypical antipsychotics considering side effects[88]. Still, isolated cases of olanzapine-induced clinical seizure have been reported[89, 90]. With multiple seizure risk factors, it is of crucial importance that TMS investigators carefully screen for medications and other potential seizure precipitants. The most recent case was an unmedicated youth with major depressive disorder treated with deep TMS[68]. Deep TMS uses H-coils that induce an effective field at a wider depth l compared to standard figure-8 TMS coils[91]. Generalized seizures in adults, as well as typical mild adverse events, have been reported during deep TMS simulation similarly as figure-8 coil stimulation[92]. However, deep TMS technology is new and continuous surveillance is needed due to its particular mode of action.

In regards to other moderate adverse events, the two cases of neurocardiogenic syncope were associated with pre-existing circumstances that would induce syncope. Of the two children, one failed to intake any food prior to the application and had a prior history of syncope with venipuncture, and the other had a history of early-morning presyncope with micturition and anxiety attacks[21, 93]. Noted as the most common adverse event related with either TMS or TBS in our literature search, mild transient headaches have been shown to be a relatively frequent side-effect of TMS and are easily quelled with acetaminophen or nonsteroidal anti-inflammatory medications[94]. Finally, local discomfort as well as neck or arm stiffness/pain, tingling, nausea/dizziness, anxiety and discomfort are also common transient mild side-effect of TMS[95].

We report one study in epileptic children where TMS induced an increase in seizure frequency up to 3 days after TMS in four children based on a phone questionnaire administered to the parents[48]. Epilepsy is a chronic brain disorder characterized by recurrent seizures. Current seizure frequency scales are based from continuous EEG monitoring during hospital stay. Patient or parent report questionnaires have raised concerns about their accuracy[96]. In the aforementioned study, children were experiencing baseline seizures at frequencies ranking from continuous to 3 per month. How accurate is a self-report of a transient increase in seizure frequency in the cases of continuous seizures or baseline seizures occurring less than once a week? The use and report of standardized scales for seizure frequency (and possibly severity) would help weighting the real adverse effect of TMS in epileptic populations.

In this review, we demonstrated that both children and adults seem to experience similar adverse events during TMS experiments. Nonetheless, because neuronal networks

are the targets of the resulting electrical currents induced during the transcranial magnetic stimulation, the effects on a developing brain should be monitored carefully; the safety of TMS in child populations may thus be contemplated independently of the safety considerations in adult populations. A good example is the MEP threshold, directly related to the degree of myelination of the corticospinal tracts (i.e. the less myelinated the tracts, the higher the threshold), which decreases with age[97]. So, with higher motor thresholds, rTMS trials on children may be conducted at much higher output power than in adults. Adult safety guidelines on the maximum intensity may then not be appropriate for children. We suggest safety measures for children to be established through brain measures of activation and connectivity at different exposure levels (i.e. single sessions vs repetitive stimulations) as previously done in adults[98, 99]. Because of the temporal resolution required to assess the immediate brain changes associated with TMS or TBS, only a few modalities are able to investigate this simultaneously. Those include fMRI, EEG, MEG or functional near infrared spectroscopy. While it is not expected to include these measures in every TMS/TBS study involving children, it may be possible to monitor short and long-term effects through cognitive and behavioral assessments. While local IRBs may impose yearly reports for AEs, other changes might not be monitored by investigators yet. We suggest systematic surveys/reports to be filled out on a session-basis to monitor potential changes in behavior, health, quality of life and adverse events. These mainly include children-oriented evaluations such as The Child Behaviour Checklist[100], the Child Health and Illness Profile[101] and the Pediatric Adverse Event Rating Scale[102]. Children with epilepsy may also add the Hague Seizure Severity Scale[103].

Pitfalls from conducting an exhaustive safety review for TMS use in children: First, safety data is not reported in a systematic manner which may lead to diverse biases. Under the FDA's revised reporting requirements in 21 CFR § 882.5805/8, investigators must immediately report any serious AEs, but mild to moderate AEs are reportable to the local IRB depending on local guidelines. This results in a lack of AEs assessment and retrieval as well as incomplete data in some cases. Second, we report and grade AEs according to the most current guidelines (CTCAE v4.0; [20]) which was originally designed for cancer drug trials. While pediatric oncologists raise the flag on its deficiencies[104] , pediatric clinicians and researchers outside of the field of cancer may find it inappropriate. Third, efficacy and safety guidelines were addressed and published in a single paper a couple of decades ago[17]. This included statements that indeed were revised such as "Children should not be used as subjects for rTMS without compelling clinical reasons, such as the treatment of refractory epilepsy or depression". There is an urgent need of criteria and guidelines applicable to children with or without epilepsy, neurological disorders and other medical conditions, as well as a systematic reporting system of AEs occurring in TMS laboratories. In this systematic review, we focused on accuracy and hope that biases from all the aforementioned issues did not deviate our main findings. In addition, we hope that this review combined with the most recent ones will help establishing appropriate guidelines for the use of TMS in children.

CONCLUSION

Over the past 30 years, over 4000 children with or without neuropsychiatric diseases have

been involved in different TMS paradigms. The induction of seizures appears to be quite rare and most reported adverse events are benign. Experiments including children with epilepsy or psychiatric disorders may still require additional clinical guidance, especially screening for at-risk medications and potential seizure precipitants. Overall, the risk of TMS appears to be similar to that in adults but as the numbers of children tested increases, there is a strong need for establishing reliable guidelines applicable to pediatric populations.

Figure legends

Figure 1: Number of publications each year focusing on sp/ppTMS (black), rTMS (dark gray) and TBS (light gray).

Figure 2: Flow chart using the PRISMA statement for the systematic review.

Figure 3: Frequencies per grade of adverse event, per modality, and per population. Circle size is representative of AE frequency per session for sp/ppTMS (black), rTMS (dark gray) and TBS (light gray).

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https://www.ncbi.nlm.nih.gov/pubmed/18811703	Kuhnke et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/18295455	Lappchen et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/18053763	Yayla et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/18196201	Heise et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/18759336	Marelli et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/19294597	Juenger et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/18684310	Redman et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/18043504	Berweck et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/18214452	Vry et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/18422835	Muralidharan et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/19086697	Uozumi et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/17593127	Valle et al.	2007	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/17389898	Jardri et al.	2007	rTMS

https://www.ncbi.nlm.nih.gov/pubmed/17719015	Buchmann et al.	2007	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/17588810	Gilbert et al.	2007	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/17382585	Guzzetta et al.	2007	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/17444535	Eyre et al.	2007	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/17627085	Kimiskidis et al.	2007	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/17121743	Siniatchkin et al.	2007	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/17188003	Kamida et al.	2007	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/16630205	Loo et al.	2006	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/16644277	Fregni et al.	2006	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/16674759	Rinalduzzi et al.	2006	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/16690208	Moll et al.	2006	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/16776434	Anninos et al.	2006	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/16760197	Gilbert et al.	2006	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/16815631	Buchmann et al.	2006	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/16864822	Dueget et al.	2006	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15564059	Morales et al.	2005	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/15607602	Staudt et al.	2005	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15794178	Perritti et al.	2005	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15979402	Garvey et al.	2005	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15984026	Bender et al.	2005	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15953499	Gilbert et al.	2005	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/16010059	Sahota et al.	2005	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15016013	Graff-Guerrero et al.	2004	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/15122428	Brasil-Neto et al.	2004	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/15003756	Dachy et al.	2004	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15036427	Kao et al.	2004	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15324826	Tataroglu et al.	2004	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15562409	Staudt et al.	2004	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15890159	Kimiskidis et al.	2004	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/16206975	Staudt et al.	2004	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15077239	Gilbert et al.	2004	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15127311	Mall et al.	2004	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15174827	Carlstedt et al.	2004	sp/ppTMS

https://www.ncbi.nlm.nih.gov/pubmed/12689695	Oguro et al.	2003	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/12948795	Garvey et al.	2003	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/14499742	Vandermeeren et al.	2003	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/14580601	Buchmann et al.	2003	sp/ppTMS
http://brain.oxfordjournals.org/content/125/10/2222	Staudt et al.	2002	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/11897533	Dachy et al.	2002	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/12088086	Rutten et al.	2002	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/12395132	Vandermeeren et al.	2002	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/12455860	Maegaki et al.	2002	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/11870691	Tshala-Katumbay et al.	2002	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/11459685	Garvey et al.	2001	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/11261515	Moll et al.	2001	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/11408329	Shimizu et al.	2001	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/11428513	Collado-Corona et al.	2001	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/11506408	Roricht et al.	2001	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/11261506	Thickbroom et al.	2001	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/11303768	Hamzei et al.	2001	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/11701594	Dobson et al.	2001	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/11706088	Eyre et al.	2001	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/11785502	Garvey et al.	2001	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/11723265	Manganotti et al.	2001	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/10825702	Manganotti et al.	2000	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/10825709	Santoro et al.	2000	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/11043527	Shimizu et al.	2000	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/11108505	Ucles et al.	2000	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/11118802	Noguchi et al.	2000	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10738920	Dan et al.	2000	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10771177	Moll et al.	2000	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10795559	Fietzek et al.	2000	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/11022138	Ertas et al.	2000	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10203149	Maegaki et al.	1999	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10024139	Heinen et al.	1999	sp/ppTMS

https://www.ncbi.nlm.nih.gov/pubmed/10319880	Mayston et al.	1999	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10372901	Nezu et al.	1999	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10479033	Nezu et al.	1999	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10507537	Moll et al.	1999	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10514585	Karak et al.	1999	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10533116	Yasuhara et al.	1999	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10590956	Moll et al.	1999	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/11003066	Inghilleri et al.	1998	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9506553	Meyer et al.	1998	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9572251	Di Lazzaro et al.	1998	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9585354	Heinen et al.	1998	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9743265	Cincotta et al.	1998	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9806140	Heinen et al.	1998	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9853705	Reitz et al.	1998	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9741799	Nezu et al.	1998	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9105661	Nezu et al.	1997	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9134188	Nezu et al.	1997	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9286189	Ziemann et al.	1997	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9389236	Tamer et al.	1997	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9392569	Muller et al.	1997	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10728200	Maegaki et al.	1997	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9266555	Maegaki et al.	1997	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/8648332	Yokota et al.	1996	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/8879655	Nezu et al.	1996	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/8880692	Nezu et al.	1996	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/8902719	Perretti et al.	1996	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/8739408	Ucles et al.	1996	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/8997449	Carr et al.	1996	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/8892376	Heinen et al.	1996	TMS
http://www.ncbi.nlm.nih.gov/pubmed/7625552	Masur et al.	1995	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/7587914	D'Annunzio et al.	1995	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/8545718	Kitagawa et al.	1995	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/8719747	Gacson et al.	1995	sp/ppTMS

http://www.ncbi.nlm.nih.gov/pubmed/8848203	Maegaki et al.	1995	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/8363351	Reutens et al.	1994	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/8747423	Imai et al.	1994	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/7512917	Glocker et al.	1994	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/7924067	Shizukawa et al.	1994	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/8190300	Haug et al.	1994	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/7679632	Caramia et al.	1993	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/8423883	Reutens et al.	1993	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/1293281	Hicks et al.	1992	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/1373370	Muller et al.	1992	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/2065752	Muller et al.	1991	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/1773779	Hufnagel et al.	1991	TMS
http://www.ncbi.nlm.nih.gov/pubmed/2273410	Hufnagel et al.	1990	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/3202641	Koh et al.	1988	sp/ppTMS

Table 1: Description of all the studies meeting search criteria. Rows color codes: White – No Adverse Event (AE); Lightest Gray – AE Not mentioned; Middle Gray – No access to screen
Dark Gray – Adverse Events assessed and subjected to analysis.

sp/ppTMS							
Author	**Year**	**No. of Individuals**	**Age (yrs)**	**Phenotype**	**TMS Mode**	**Paradigm and Target**	**Adverse Events**
Hong et al., 2015	2015	89	6-18	19 Tourette's 70 Control	sp/ppTMS Figure 8 Coil	MEP, RMT (60% & 120%, AMT, CSP Approximately 200 pulses per part. Target: Motor Cortex	Mild: Headache (6), scalp pain (4), arm/hand/other pain (2), numbness/tingling (5), other sensations (1), nausea/vomiting (1), other (1). Moderate: Ringing in ears (1).
Damji et al.	2015	28	6-18	Healthy	spTMS Figure 8 Coil	100-150% RMT, 0.2Hz, 7.5min Target: Motor Cortex	Mild: Neck pain (1), headache (3), transient nausea (2).
Wu et al.	2012	114	8-12	64 Control 50 ADHD	sp/ppTMS Figure 8 Coil	20 sp trials set at 15-30% over RMT. ppTMS of 70% RMT. Target: Motor Cortex	Mild: Discomfort (15).
Geerdink et al.	2012	78	6-15	36 Control 42 Spina Bifida	sp/ppTMS Double Cone Coil	100% stimulation intensity MEP. Target: Motor Cortex	Mild: Discomfort (12) in controls, as well as an undisclosed number in Spina Bifida population.
Koudijs et al.	2010	34	3-18	Epileptic	sp/ppTMS	Intensity was titrated until MEP – up to max of 4T.	Increase in seizure frequency that subsided after three days with no intervention (4).

					Round Coil and Figure 8 Coil	Target: L/R Motor Cortex	
Kirton et al.	2010	4	10-16	Arterial Ischemic Stroke Lesions	spTMS ppTMS Figure 8 Coil rTMS	110 to 150% RMT or 100% MSO when no RMT 6 stimuli per level, 36 stimuli per side Target: contralateral motor cortex 100% RMT 8 days, 1 Hz 20min	Mild: Headache (2), neck stiffness (3), nausea (3). Moderate: Neurocardiogenic syncope (2).
Gilbert et al.	2006	16	8-17	ADHD	sp/ppTMS Circular Coil	RMT, AMT, SICI, ICF. All TMS sessions took approximately 30 minutes. Target: Motor Cortex	Mild: Numbness/tingling (2), loss of appetite (2), scalp pain (1), nausea (2), stomach pain (1) and headache (5), arm/other pain (2), abdominal pain (1), hearing change (1). Moderate: Headache (1).
Bender et al.	2005	17	6-10	Healthy	sp/ppTMS	105% RMT for MEPs, when RMT>MSO intensity was set to 100%. Target:	Mild: Discomfort (1).

					Circular Coil	Right Motor Cortex	
Gilbert et al.	2004	28*	< 18	Tourette's Syndrome (w/ ADHD/OCD in some cases)	sp/ppTMS Circular Coil	MEP, ISI, SICI, CSP at 130% AMT Target: Motor Cortex	Mild: Discomfort (3), scalp pain (5), tiredness (4), hand or leg tingling (3), hand weakness (2), headache (1), and neck pain (1).
Shizukawa et al.	1994	1	16	Hirayama Disease	spTMS	MEP Target: Motor Cortex	Mild: Dullness (1).

TBS							
Author	**Year**	**No. of Individuals**	**Age (yrs)**	**Phenotype**	**TMS Mode**	**Paradigm and Target**	**Adverse Events**
Hong et al.	2015	76	6-18	52 Control 24 Tourette's Syndrome	TBS MagStim Rapid 2	60-90% RMT. Three pulses at 30-50Hz, 5Hz burst freq. w/ total stimuli 300-600.	Mild: Headache (5), numbness/tingling (2), other sensations (2), weakness (1), arm/hand/other pain (1), other (1). Moderate: Arm/hand/other pain (1).
Wu et al.	2012	40	11-18	24 Control 16 Tourette's Syndrome	iTBS & cTBS Figure 8 type coil	50Hz, 80% active MT or 90% RMT 32 sessions Target: Left Motor Cortex.	Mild: Finger twitching (1), neck stiffness (1), headache (3).

rTMS

Author	Year	No. of Individuals	Age (yrs)	Phenotype	TMS Mode	Paradigm and Target	Adverse Events
Cullen et al.	2016	1	17	Treatment Resistant Depression	Deep TMS H-1 Coil	18 Hz, 120% MT, 55 trains, 1980 pulses total.	Moderate: Generalized, tonic-clonic seizure that lasted 90 seconds and resolved spontaneously (1).
Kirton et al.	2016	45	6-19	Hemiparesis	rTMS	1 hz, 20 min 1200 stim, 1200 stimuli per session, once a day, 5 days/week, 2 weeks total. Target: Contralesional M1	Mild: Headache (4), nausea (1), tingling (1).
Gillick et al.	2015	10	8-17	Congenital Hemiparesis	rTMS Figure 8 Coil	6 Hz, 90% RMT, 2 5s trains/minute (total 600 pulses). Followed by 10 minutes of 1Hz, 90% RMT(600 pulses). Target: Contralesional Motor Cortex	Mild: Headache (5), anxiety (3), dizziness (2), tingling (2).
Pathak et al.	2015	13	12-17	Bipolar Mood Disorder	rTMS	20 Hz, 110% MT 800 daily pulses, 10 days Target: Right Prefrontal	Mild: Headache (2)

					Figure 8 Coil	Cortex	
Christancho et al.	2014	1	15	Autism	rTMS	90% of the RMT, 1 Hz, 10 seconds on, and 10-30 seconds off. 30 sessions in total. Target: L/R DLPFC	Mild headaches during half of the sessions. Dizziness and jaw twitching also occurred.
Gomez et al.	2014	10	7-12	ADHD	rTMS Butterfly Coil	90% RMT, 1Hz. 1500 stimuli/session. 1 session/day. 5 days. Target: L-DLPFC	Mild: Headache (7), neck pain (2), dizziness (2).
Panerai et al.	2014	35	11-18	Autism	rTMS Figure 8 Coil	90% RMT, 1Hz train (900 pulses), and 30 8Hz trains of 30 stimuli. Target: L/R Premotor Cortex	Mild: Restlessness (1). Moderate: Rapid moodswings (1)
Gillick et al.	2014	10	8-17	Congenital Hemiparesis	rTMS	6 Hz, 90% RMT, 2 5s trains/minute (total 600 pulses). Followed by 10 minutes of 1Hz, 90% RMT(600	Mild: Headache

					Figure 8 Coil	pulses). Target: Contralesional Motor Cortex	
Yang et al.	2014	6	15-21	Major Depressive Disorder	rTMS Figure 8 Coil	120% RMT, 10 Hz, 75 trains (3000 pulses) Target: Left DLPFC	Mild: Scalp discomfort, sleepiness
Chiramberro et al.	2013	1	16	Major Depressive Disorder	rTMS Figure 8 Coil	10 Hz, 120% RMT 3000 daily pulses 4 weeks of 60 trains of 5 s, 5 days/week Target: Left DLPFC	Moderate: Tonic-clonic seizure of 30 sec on 12th day of rTMS. Patient was taking sertraline and olanzapine, and also had a high blood alcohol content.
Le et al.	2013	25	7-16	Tourette's Syndrome	rTMS Figure 8 Coil	110% RMT, 1 Hz, 20 daily sessions (1200 stimuli daily). Target: Supplementary Motor Area	Mild: Sleepiness (1).
Helfrich et al.	2012	25	8-14	ADHD	rTMS Figure 8 Coil	80% RMT, 1 Hz (900 stimuli). Target: Left Motor Cortex	Mild: Headache (3)
Croarkin et al.	2012	8	14-17	Major Depressive	rTMS	120% MT, 10Hz, 4s	Mild: Scalp pain (1).

				Disorder		trains (3,000 stimuli per session). Target: Motor Cortex	
Hu et al.	2011	1	15	Adolescent Onset Depressive Disorder	rTMS Figure 8 Coil	10 Hz, 80% RMT 800 daily pulses Target: Left DLPFC	Moderate/Severe: Tonic-clonic seizure of 1min on 1st day of rTMS, and hypomanic episode the night following the seizure. Patient follow-up indicated no further seizure. Patient was taking sertraline.
Kwon et al.	2011	10	9-14	Tourette's Syndrome	rTMS Figure 8 Coil	100% RMT, 1 Hz (1,200 stimuli daily for ten days). Target: Supplementary Motor Area	Mild: Scalp pain (1).
Bloch et al.	2008	9	16-18	Severe Resistant Depression	rTMS Circular Coil	80% MT, 10-Hz, 2s trains given over 20 min/d over 14 working days.	Mild: Headache (5).

Table 2: Description of adverse events. Rows color codes: Lightest Gray – Mild AEs (or Grade 1); Middle Gray – Moderate AEs (or Grade 2); Dark Gray – Sever AEs (or Grade 3).
* Number of adolescent participants is exact, whereas number of adverse events is from the entire population of the study (n=36).