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Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Depression in Adolescence: A Systematic Review

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**Introduction**

Depression is the fourth leading cause of illness and disability among young people aged 15–19 years old . Worldwide, prevalence rates of depression among young people are estimated to be between 5.6–6.7% (Bromet et al., 2011; Costello, Erkanli, & Angold, 2006); a rate which has increased over the last decade (Fink et al., 2015; Patalay & Gage, 2019). At present, the reasons behind the increase in reported depressive symptoms remain unclear. However, researchers propose that it may be due to the rise of digital media use and declines in sleep duration (Twenge, Cooper, Joiner, Duffy, & Binau, 2019). Lifetime prevalence of depression is high among adult populations (20.6%) (Hasin et al., 2018). However, the first onset of depression is likely to occur during the adolescent period (Thapar, Collishaw, Pine, & Thapar, 2012), with adolescent depression associated with poor educational attendance (Fletcher, 2008), relationship problems (Vujeva & Furman, 2011) and an increased risk of suicidal ideation and behaviour (Lewinsohn, Rohde, & Seeley, 1994). Adolescent depression also predicts several negative health outcomes in later life, including physical health problems (Bardone et al., 1998), anxiety disorders and bipolar disorder (Copeland, Shanahan, Costello, & Angold, 2009; Fergusson, Horwood, Ridder, & Beautrais, 2005; Kim-Cohen et al., 2003). Thus, there is a strong clinical need for effective interventions in this area. However, current treatment options for young people with depression remain limited.

Although treatment practice for adolescent depression varies across different countries, young people will typically be offered psychological treatments (e.g., cognitive behavioural therapy; CBT) and/or antidepressant medication (i.e., a selective serotonin re-uptake inhibitor; SSRI) (Thapar et al., 2012), namely fluoxetine as, to date, this medication has the greatest evidence for efficacy in this population (Hetrick, Merry, McKenzie, Sindahl, & Proctor, 2007; NICE, 2015). CBT is an effective treatment for depression, with meta-analyses yielding moderate effect sizes for adolescent depression treatment (Klein, Jacobs, &

Reinecke, 2007). However, long waiting times and a reluctance to commit to prolonged psychological therapy are identified as barriers to young people accessing psychological support for their depression (Kowalewski, McLennan, & McGrath, 2011; Young Minds, 2018). There is concern about anti-depressant use in young people. Firstly, whilst SSRI's can be effective, antidepressants are linked to an increased risk of suicidal ideation and behaviour in young people (Cipriani et al., 2016). Antidepressants are also associated with side effects such as weight gain/loss, increased anxiety, insomnia and poor appetite (Ferguson, 2001). As such, there remains an urgent clinical need to develop effective and safe alternate and/or complimentary treatment options for young people with depression.

Transcranial magnetic stimulation (TMS) is a form of non-invasive brain stimulation in which a changing magnetic field alters the activity in neural circuits in the brain, such as those in the dorsolateral prefrontal cortex (DLPFC) implicated in the pathophysiology of depression. TMS does not require anaesthesia or hospital inpatient admission and there does not appear to be debilitating side-effects in adults as associated with antidepressants (Penn & Tracy, 2012). Protocols that enable pulses of TMS to be delivered in short intervals are referred to as repetitive TMS (rTMS) (Barker, Jalinous, & Freeston, 1985; Klomjai, Katz, & Lackmy-Vallee, 2015). High-frequency rTMS (> 1 Hz) is thought to have an excitatory effect on the cerebral cortex, whereas low-frequency rTMS (≤ 1 Hz) is thought to have an inhibitory effect, with rTMS believed to modulate the function of stimulated region beyond the period of stimulation. Such protocols are increasingly being used for therapeutic purposes, with both high- and low-frequency rTMS used to treat adults with depression by stimulating the DLPFC (Berlim, Van den Eynde, & Jeff Daskalakis, 2013; George et al., 2000), altering the neural activity within brain circuits implicated in the pathophysiology of depression (Iwabuchi et al., 2014; Liston et al., 2014). rTMS is found to be therapeutically effective and able to significantly reduce the burden of depressive symptoms in adults.

Consequently, rTMS is approved by the US Food and Drug Administration (FDA) as a treatment for major depression in adults (O'Reardon et al., 2007), however, the evidence for its use in adolescents with depression remains unclear. This review paper seeks to address this knowledge gap.

To date, several reviews have suggested that rTMS offers an attractive option as a safe and effective treatment for adolescent depression (Croarkin & MacMaster, 2019; Croarkin et al., 2010; D'Agati, Bloch, Levkovitz, & Reti, 2010; Donaldson, Gordon, Melvin, Barton, & Fitzgerald, 2014; Magavi, Reti, & Vasa, 2017) . Whilst important, none of this previous work has used a systematic review methodology to examine the extant literature. Also, several multi-subject trials have been published since the last review (Magavi et al., 2017). An up-to-date systematic review is warranted to guide researchers and clinicians. Here, we examine all existing literature regarding the use of rTMS for adolescent depression to address two research questions: 1) how effective is rTMS in treating adolescent depression and, 2) what are the reported side effects of rTMS treatment for adolescent depression?

**Methods**

We followed the PRISMA guidelines (Liberati et al., 2009) using systematic review methodology outlined by Cochrane (Higgins et al., 2019). We pre-registered our review protocol  on PROSPERO (ID: CRD42020177490; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=177490). A systematic search was conducted on the following databases: PubMed, Embase, PsycINFO, Web of Science and the Cochrane Central Register of Controlled Trials (CENTRAL), to identify studies which utilised rTMS in adolescent depression. The search terms ("repetitive transcranial magnetic stimulation" OR rTMS OR TMS) AND (depression OR emotional disorder) AND (adolescen* OR child* OR young OR teen*) were entered. Please see

Supplementary Material Table 3 and Figure 1 for details of the search strings used. Studies from the year January 2000 up to and including 30th April 2020 were included in the search.

We augmented this process by searching: 1) the reference lists of previous rTMS review papers (Croarkin et al., 2010; D'Agati et al., 2010; Donaldson et al., 2014; Magavi et al., 2017), 2) clinical trial registers (i.e., ClinicalTrials.gov) for any current rTMS trials, 3) consulted with experts in the field for knowledge of any relevant ongoing trials, 4) searched the first 30 pages of Google Scholar and, 5) hand searched the last two years of three journals which commonly publish rTMS studies for depression (i.e., *The Journal of Child and Adolescent Psychiatry, The Journal of Affective Disorders* and *Frontiers in Psychiatry*).

*Inclusion and exclusion criteria*

Inclusion criteria were: 1) Any study (e.g., controlled, uncontrolled, observational and before and after design) that utilised an rTMS intervention (intensity, frequency, target area, dose and duration not limited) to treat adolescent depression; 2) Studies that included young people with a mean age range of 12–25 years old; 3) Studies that included young people with a clinical diagnosis of depression; 4) English language studies.

Exclusion criteria were: 1) Studies that only assessed adult populations, or, in studies that assessed both adults and adolescents, we excluded those which neglected to analyse the adolescent cohort separately; 2) Studies that did not adopt an rTMS protocol (e.g., single-pulse TMS) or utilised other non-invasive brain stimulation approaches (e.g. transcranial direct current stimulation; tDCS).

*Article screening/review process*

Figure 1 outlines the literature search in the form of a PRISMA diagram. After the removal of duplicates, 1142 articles were screened at the title and abstract stage by two

independent researchers (DH & CH) using the inclusion/exclusion criteria. Disagreements, as well as any articles that appeared unclear at this screening stage, were resolved via discussion with a third independent researcher, until 100% agreement was achieved. This resulted in the retrieval of 69 outputs which underwent full-text assessment, of which 14 published studies were included in this review (see Table 1). The database searches also revealed 5 conference abstracts which appeared suitable for inclusion. In these instances, we contacted the authors and asked for more information on their abstract to ascertain whether this was a new (e.g., unpublished) rTMS trial, or, whether the study utilised data from an existing published rTMS trial. Four of these abstracts were confirmed to be unpublished studies, all which had conducted secondary data analysis from an open-label trial already included in this review (MacMaster et al., 2019), and were thus excluded. However, one abstract was confirmed to be a new (unpublished) rTMS intervention (Lee et al., 2019) and so we have included information about this study in the discussion, under the *recommendations for future research* section. Table 1 summarises the final 14 studies included in the review, including information on sample characteristics, rTMS intervention protocols and the overall outcome of the study.

*Risk of bias assessment*

The Newcastle-Ottawa Quality Assessment Scale (NOS) (Wells et al., 2014) was used to assess the quality of the final included studies (N = 14). The NOS is a Cochrane recommended tool to assess quality or risk of bias in non-randomised studies (Higgins et al., 2019) and has been used previously in reviews including pre-post design studies (e.g., (Ganapathy, Adhikari, Spiegelman, & Scales, 2012). It assesses three quality parameters: selection, comparability and outcome. The maximum score awarded from the NOS is 9 across the three parameters: 1) selection (four points), 2) comparability (two points) and 3)

outcome (three points). The higher the score, the higher the quality of the study (i.e., lower risk of bias). A total score for each study is then converted into an overall quality rating of either, poor, fair or good quality. Scores of 0–3 were considered low quality, 4–6 moderate quality and 7–9 high quality. Two reviewers (DH and CH) independently assessed the quality of the included studies (see Supplementary material Table 1 and 2 for the NOS criteria and summary table).

[insert Figure 1 near here]

**Results**

*Summary of included studies*

Table 1 outlines the study characteristics of the 14 studies included in the review, 8 of these studies were open-label trial studies, totalling N = 142 adolescent participants with depression receiving rTMS treatment (Bloch et al., 2008; Croarkin et al., 2016; Dhami et al., 2019; MacMaster et al., 2019; Rosenich et al., 2019; Wall et al., 2011; Yang et al., 2014; Zhang et al., 2019). The remaining 6 studies were either post-hoc analyses studies (using these existing open-trial datasets) (n = 5 studies) (Croarkin et al., 2018; Croarkin et al., 2012; Sonmez et al., 2019; Wall et al., 2016) and one study (Mayer, Aviram, Walter, Levkovitz, & Bloch, 2012) was a three-year follow-up of one of the open-trial studies (see Table 1 for specific details of datasets used in these studies).

Studies were conducted in the USA (n = 7), Canada (n = 3), Israel (n = 2), China (n = 1), and Australia (n = 1). All studies were published within the last 12 years, with five studies published in 2019 alone; this demonstrates the growing interest in the use of rTMS for treatment of adolescent depression. Overall, all included studies reported that high-frequency rTMS (> 1 Hz) demonstrated a beneficial effect at reducing symptoms of depression in adolescents.

Further, upon searching ClinicalTrials.gov, we found 16 relevant registered clinical trials. 8 of these referred to trials which have either been terminated (n = 3) or were trials already found in our search (i.e., published studies; n = 5), leaving 8 trials that are currently ongoing. No new studies were obtained from: 1) cross-referencing previous relevant review papers, 2) contacting authors in the field, 3) handsearching three key journals in the field or 4) Google Scholar search.

*Study designs*

The eight trial studies were all open-label multi-subject trials. Consequently, there were no controlled trial studies which included an active comparator or a control group (e.g., sham-control).

*Samples*

Sample sizes varied across the included studies from 6–42 participants (see Table 1). Thirteen studies included adolescents with a diagnosis of treatment-resistant depression (TRD) (Bloch et al., 2008; Croarkin et al., 2018; Croarkin et al., 2016; Croarkin et al., 2012; Dhami et al., 2019; MacMaster et al., 2019; Mayer et al., 2012; Rosenich et al., 2019; Sonmez et al., 2019; Wall et al., 2016; Wall et al., 2013; Wall et al., 2011; Yang et al., 2014) and only one study included adolescents diagnosed with *either* a mood or anxiety disorder (i.e., not TRD) (Zhang et al., 2019). At baseline, all these clinical diagnoses were verified in line with the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) criteria (APA, 2000) using either the Mini-international Neuropsychiatric Interview (Sheehan et al., 1998) or the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime version (K-SAD-PL) (Kaufman et al., 1997). From the 13 studies that assessed TRD, the most common definition of TRD was at least one failed treatment attempt using

antidepressants (Bloch et al., 2008; Croarkin et al., 2018; Croarkin et al., 2016; Dhami et al., 2019; MacMaster et al., 2019; Mayer et al., 2012; Sonmez et al., 2019; Wall et al., 2016; Wall et al., 2013; Yang et al., 2014). Two studies defined TRD as two failed attempts using antidepressants (Croarkin et al., 2012; Wall et al., 2011) and one failed to report the definition (Rosenich et al., 2019). Participants from all studies apart from one (Yang et al., 2014) were reported to be taking antidepressant medication (e.g., SSRI) and/or receiving psychotherapy for their depression, alongside their participation in the rTMS study. Upon recruitment, the open-trial studies excluded participants with a history of psychiatric (e.g., schizophrenia, schizoaffective, bipolar, PTSD), substance abuse and neurological disorders, as well as those with history of epilepsy and seizures as contraindications for rTMS. However, current co-morbidity with other internalising (e.g. anxiety) or externalising (e.g. ADHD) disorders was not an exclusionary criterion, with some participants diagnosed with depression alongside other psychiatric disorders.

*rTMS protocols*

Most studies adopted a high-frequency rTMS stimulation procedure alone (n = 12), with only one study employing theta-burst stimulation (TBS) (Dhami et al., 2019) (a newer modality of rTMS in which relatively greater amounts of stimulation can be delivered in a shorter span of time) and one study using both high (10 Hz) and low (1 Hz) frequency rTMS (Rosenich et al., 2019). In Dhami et al. (2019), pulses were administered in the theta-frequency range of 1800 pulses to left DLPFC (L-DLPFC) and 1800 pulses to right DLPFC (R-DLPFC). High-frequency rTMS (10 Hz) at 120% motor-threshold (MT), administered with a 4 second train and a 26 second interval, applied to the L-DLPFC was the most common rTMS treatment protocol adopted (n = 8 in total; n = 4/8 open-trial studies). Two studies (Dhami et al., 2019; Rosenich et al., 2019) administered rTMS to both the L- and R-

DLPFC. For instance, in Rosenich et al. (2019), one group was administered 15 minutes of high-frequency rTMS (10 Hz) to the L-DLPFC, immediately followed by low-frequency (1 Hz) to the R-DLPFC. Whereas in Dhami et al. (2019), all participants received intermittent and continuous TBS stimulation to the L- and R-DLPFC respectively.

Most (n = 6) open-trials studies administered treatment sessions within the range of 10–20 sessions (Bloch et al., 2008; Dhami et al., 2019; MacMaster et al., 2019; Rosenich et al., 2019; Yang et al., 2014; Zhang et al., 2019) whereas, two trials delivered up to 30 sessions (Croarkin et al., 2016; Wall et al., 2011). A range of methods were used to localise the anatomical site; including the 5/6cm Rule (Bloch et al., 2008; Croarkin et al., 2012; Mayer et al., 2012; Rosenich et al., 2019; Wall et al., 2011), neuro-navigation using a structural MRI (magnetic resonance imaging) brain scan (Croarkin et al., 2016; Dhami et al., 2019), or a combination of both (Croarkin et al., 2018; MacMaster et al., 2019; Sonmez et al., 2019; Wall et al., 2016; Wall et al., 2013; Yang et al., 2014).


*Outcomes investigated*

Depression symptoms across the included studies were assessed using validated tools; namely the Hamilton Depression Rating Scale (Hamilton, 1960) the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski et al., 1984) (both clinician administered tools). In addition to overall depression symptoms, some of the post-hoc studies analysed additional outcomes related to depression/ rTMS. For instance, two post-hoc analysis studies analysed the impact of rTMS on two specific depression symptoms: 1) sleep disturbances (i.e., insomnia and hypersomnia) (Sonmez et al., 2019), as measured via the Quick Inventory of Depressive Symptomology-Adolescent (QIDS-A) (Bernstein et al., 2010) and, 2) suicidal ideation (Croarkin et al., 2018), as measured via the Columbia Suicide Severity Rating Scale "intensity of ideation" subscale (C-SSRS) (Posner et al., 2011). The C-SSRS subscale is

comprised of 5 items (frequency, duration and controllability of ideation, deterrents and reason for ideation). The remaining three post-hoc analysis studies investigated: 1) the effects of different localisation techniques in rTMS treatment (Wall et al., 2016); 2) neurocognitive effects of rTMS (Wall et al., 2013); 3) motor cortical excitability in rTMS treatment (Croarkin et al., 2012). Given that the aim of this review is to explore the effectiveness and feasibility of using rTMS in treating adolescent depression, we will discuss points 1 and 2 above in this review but not point 3 (underlying neural mechanisms of action of rTMS).

[Table 1 near here]

*Risk of bias and methodological quality of studies*

We measured the quality of each study using the NOS (see Table 2 of the supplementary material). The mean study quality score for the included studies was 4.71 (*SD* = 0.47), out of 9, representing moderate quality. Importantly, none of the studies included a comparator group such as a control group, thus, it remains unclear whether the reduction in depression symptoms reported in these studies is due to the effects of rTMS alone or as a result of biases/a placebo effect. Secondly, some studies lost a large proportion (i.e., > 20%) of participants at follow-up and/or neglected to describe reasons why, and thus lost points in the quality assessment. In sum, the studies reviewed in this current review are either of poor or fair quality, meaning there was a high risk of bias in their design or reporting.

*How effective is rTMS at reducing depression symptoms in adolescents?*

All 14 studies reported that rTMS had some effect at reducing symptoms of depression in adolescents. Five studies reported that rTMS statistically significantly reduced

depression symptoms as measured by the HAM-D (Dhami et al., 2019; MacMaster et al., 2019; Rosenich et al., 2019; Yang et al., 2014; Zhang et al., 2019). For instance, both Rosenich et al. (2019) and Macmaster et al. (2019) utilised pre-post intervention study designs. Rosenich et al (2019) conducted a six-week open-label rTMS trial where they assessed the efficacy of three different treatment protocols (see Table 1) in adolescents with TRD. They also compared the results of the adolescent open-label trial to data collected from adults (aged 25–82 years old) treated with rTMS, to explore whether there were any differences in response rate between age groups. Interestingly, over half of the participants in this study had failed to respond to at least five antidepressant medications previously. Response was defined as $\geq 50\%$ reduction in HAMD scores and partial response was seen as a 25–50% reduction in HAMD scores. The study revealed that over three-quarters met criteria for at least a partial response, and there was no significant difference in outcomes between young people and adults, suggesting that rTMS was equally efficacious in treating depression in both age groups. Similarly, MacMaster et al. (2019) conducted a three-week rTMS trial and found a 56% response rate (n = 18/32) (i.e., $\geq 50\%$ reduction in HAM-D scores from pre to post intervention). This is also comparable to an earlier rTMS trial which found a 68% response rate (n = 4/6) (i.e., $\geq 50\%$ reduction in HAM-D scores) in HAM-D scores (Yang et al., 2014). Only one study assessed the efficacy of TBS (Dhami et al., 2019). Dhami and colleagues (2019) recruited 20 adolescents with TRD, however 17 completed the full rTMS trial (i.e., 10 sessions of rTMS). Here, authors found a significant reduction in depression symptoms from baseline to post-treatment (i.e., after 10 sessions) ($p < .0001$), with four out of 17 participants being classified as responders (i.e., $\geq 50\%$ reduction in depression scores). Interestingly, data also showed that participants with a greater baseline anhedonia score were less likely to demonstrate improvements in depression symptoms following rTMS treatment, a finding that conforms with that from the adult rTMS literature

(Downnar et al., 2014). Lastly, Zhang et al.'s (2019) study suggested that rTMS may also be an effective first-line treatment for young people with depression. This study had the largest sample of young people from this current review (N = 42) and all participants were diagnosed with either a mood or an anxiety disorder (DSM-IV; APA, 2000). Zhang et al. (2019) compared the efficacy of rTMS as a treatment for depression among adolescents (10–18 years old), adults (18–60 years old) and older adults (aged 60 years old +), yielding a total sample of 117 participants. The majority of participants held a diagnosis of major depressive disorder (MDD) (78.63%), however it is unclear what percentage of adolescents specifically held this diagnosis. Other recorded diagnoses included bipolar disorder II, generalised anxiety disorder, obsessive compulsive disorder, eating disorder and dysthymia. All participants had up to 20 sessions of high-frequency rTMS and depression symptoms were measured throughout the trial, and at a 2-week and 4-week follow-up post rTMS. Results showed that at the 2-week and 4-week follow-up, all age groups demonstrated a significant reduction (i.e., $\geq 50\%$ reduction) in HAMD scores.

Further, Zhang et al. (2019) reported that rTMS may be more effective in adolescents compared to adult populations, as they found that the adolescent group had a greater percentage decrease in HAMD scores, compared to the adult and older adult groups. However, it is important to note that this finding was likely due to the lower baseline HAM-D scores for the adolescent group, compared to the adult groups. As this is the only study to focus on the efficacy of rTMS in young people without TRD, it still remains unclear whether rTMS would be an effective treatment for all forms of depression.

Next we turn to those studies which reported a reduction in depression symptoms as measured via the CDRS-R (n = 9) (Bloch et al., 2008; Croarkin et al., 2018; Croarkin et al., 2016; Croarkin et al., 2012; Mayer et al., 2012; Sonmez et al., 2019; Wall et al., 2016; Wall et al., 2013; Wall et al., 2011). For instance, Wall et al. (2013) pooled together existing data

from two previous open-label trials (see Table 1) and found that treatment of 30 rTMS sessions was effective at reducing depression severity in adolescents. Further, Bloch et al. (2008) reported a significant reduction in mean CDRS-R scores from baseline ($M = 71.80$, $SD = 6.30$) to post-treatment ($M = 55.20$, $SD = 14.80$), after 14 sessions.

In addition to an overall reduction in CDRS-R scores following rTMS treatment, some studies also examined specific depression symptoms. Sonmez et al.'s (2019) primary outcome variable was hypersomnia symptoms—a common symptom of MDD (Sunderajan et al., 2010). Here, authors examined the impact of rTMS on sleep disturbances (i.e., insomnia and hypersomnia) in adolescents with TRD. Results showed no significant effects for insomnia symptoms, however it appeared that hypersomnia symptoms improved from baseline to treatment session 10 ($p = .019$) and between baseline and the 6-month follow-up ($p = .044$). However, there were no significant differences found between baseline scores and treatment sessions 20 and 30 ($p$s $= .053 – .209$). Although participants were noted to either be currently taking or previously prescribed hypnotic medication throughout the rTMS intervention, it was reported that hypnotic medications did not have a significant effect on hypersomnia scores ($p = .801$). Additionally, Croarkin et al. (2018) demonstrated that rTMS may help to reduce suicidal ideation among depressed adolescents. 17 adolescents completed ratings of suicidal ideation at both baseline and post-treatment. Results showed that 10/17 (58.82%) demonstrated improvement in suicidal ideation between baseline and post-treatment. However, the authors note that this improvement was likely mediated by improvement in overall depressive symptom severity.

*Assessment of depression symptoms over time*

Some studies did include a follow-up period to assess depression symptoms. This was either a one-month (Bloch et al., 2008; Zhang et al., 2019) or a six-month follow-up

(Croarkin et al., 2016; Sonmez et al., 2019; Wall et al., 2016; Wall et al., 2013; Wall et al., 2011). Four studies either not did not include a follow-up period or failed to report it (Dhami et al., 2019; MacMaster et al., 2019; Rosenich et al., 2019; Yang et al., 2014). In both the 1 and 6-month follow-up studies, all reported that, compared to baseline depression scores, those at the follow-up were significantly lower. However, due to the lack of control group in these studies, it is hard to ascertain whether this is due to the effects of rTMS alone or other factors (e.g., recovery over time, current medication/psychotherapy; see also (Nord et al., 2019).

Mayer et al. (2012) conducted a 3-year follow-up study (N = 8) evaluating symptoms of depression and cognitive functioning in adolescents who participated in an open-trial study 3 years previous (Bloch et al., 2008). At the time of follow-up, 3 patients were not on any psychotropic medications and the rest were taking some form of medication for their mental health (e.g., antidepressants). Half of the participants had also received a course of electroconvulsive therapy (ECT) during the 3-year follow-up period. Results showed no evidence of deterioration in depression symptoms or cognitive functioning, compared to participants' last assessment (i.e., after 14 sessions of rTMS 3-years prior). The authors suggest that these results offer preliminary support for the long-lasting beneficial effects of rTMS in adolescent depression, though the underlying rationale for this claim was unclear. The lack of control group alongside the treatments delivered during the follow-up period make it hard to determine whether improved (i.e., reduced) depression scores maintained at three years were due to rTMS alone.

*Safety data in studies of rTMS in the treatment of adolescent depression*

Table 2 summarises the reported rTMS side effects from the 8 open-trial studies. Commonly reported side effects included symptoms such as headaches, mild scalp pain,

dizziness and tiredness. In addition to the reported side effects in Table 2, some participants did withdraw from the study due to a deterioration in their mental health with may or may not have been due to rTMS. For instance, increased suicidal ideation was reported by some participants in Sonmez et al. (2019), Croarkin et al. (2018) and Wall et al. (2016). However, as all 3 of these studies used post-hoc/pooled datasets, it is hard to know from which open-trial dataset these participants were in and whether this was due to the rTMS treatment or other factors.

Four studies also investigated whether rTMS poses any detrimental effects on cognitive functioning. Firstly, Wall et al. (2013) found no evidence of decline in cognitive functioning as measured via the Children's Auditory Verbal Learning Test-Second Edition (Talley, 1993) and Delis-Kaplan Executive Function System (Delis, Kramer, Kaplan, & Holdnack, 2004).This was also noted in previous work by Wall and colleagues (Wall et al., 2011; 2013). Mayer et al. (2014) followed participants up 3-years post-rTMS. Participants were asked to complete the Neuropsychological Test Automated Battery (CANTAB) (Luciana, 2003) to determine cognitive functioning as a result of previous rTMS treatment. The CANTAB measures motor speed, working memory, attention and planning. The authors found no evidence of deterioration in cognitive functioning and there appeared to be a slight improvement in measures of planning, from baseline to three-year follow-up.


[Table 2 near here]


*Unpublished/ongoing clinical trials*

Our literature search also revealed information on one completed—but unpublished—rTMS intervention trial conducted by Lee et al. (2019) (see https://clinicaltrials.gov/ct2/show/NCT03708172). In this study, Lee and colleagues (2019)

conducted a double-blind placebo-controlled feasibility study whereby adolescents (N = 26 completed), aged 16–24 years old diagnosed with major depression, received 4 weeks of combination TBS and cognitive training treatment, followed by active or sham cognitive training. Here, all participants received daily open-label TBS and there was no placebo condition for the stimulation, only the cognitive training. Authors report in the abstract that both the TBS and cognitive training was well tolerated, and mild side effects were reported, such as headache (< 8%), nausea, (< 4%) and site discomfort (< 5%). However, the effects of this combined intervention on depression symptoms is unclear. Further, we also found 8 ongoing treatment trials of rTMS for adolescent depression registered on ClinicalTrials.gov and/or CENTRAL. Five of these trials were current trials testing out low and/or high-frequency rTMS, including a double-blind randomised trial of 36 sessions of low- (1 Hz) vs-high-frequency rTMS (10 Hz) (https://clinicaltrials.gov/ct2/show/NCT03363919), as well as part 1 https://clinicaltrials.gov/ct2/show/NCT01804270 and part 2 (https://clinicaltrials.gov/ct2/show/NCT01804296 of a double-blind, randomised, sham-controlled rTMS trial. Here, the active rTMS treatment proposed is high-frequency (10 Hz). Another open-label rTMS trial https://clinicaltrials.gov/ct2/show/NCT02611206 reports investigating the effects of high-frequency rTMS (10 Hz) with varying stimulation intensities and the another investigating low-frequency rTMS (https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01871756/full). The rest of the registered trials (n = 3) report investigating TBS. The first being a NIMH 2-year, double-blind, randomised study (https://clinicaltrials.gov/ct2/show/NCT03737032) whereby all participants will receive intermittent TBS, continuous TBS or sham TBS. The next, is an open-label 6-week trial of intermittent TBS (https://clinicaltrials.gov/ct2/show/NCT03845504) and the last is a double-blind randomised deep TMS trial (https://clinicaltrials.gov/ct2/show/NCT03541707).

**Discussion**

      This review indicates that the overall quality of the literature to date in this field is inadequate, but that available studies suggest a detectable signal of efficacy for rTMS in the treatment of depression in adolescents. This signal is probably limited to young people who have failed to improve with at least one other treatment, and who are currently taking anti-depressants. Whether these effects are attributable to the treatment, due to bias or a strong placebo effect is difficult to ascertain currently. Over the past decade alone, there has been a growing interest in the use of rTMS to treat adolescent depression. This is evident in the current review, as several multi-subject trial studies have been published within the last 5 years—further highlighting the need for an updated review paper. The last review paper (Magavi et al., 2017) consisted of 15 studies, however, five of these were case reports. The present review suggests that rTMS may be a promising treatment for adolescent depression, as all of the included studies included reported that rTMS was able to reduce depression symptoms with mostly mild side effects. There has been concerns that rTMS can induce accidental seizures (Ridding & Rothwell, 2007), however the risk is estimated to be low (0.1– 0.6%) (Croarkin, Wall, & Lee, 2011). Crucially, none of these multi-subject studies reported that rTMS lead participants to have a seizure. In a previous systematic review of rTMS in adolescent depression (Magavi et al., 2017), the authors highlighted that three of their included studies reported a risk of seizure. However, importantly, these were all case report studies (Chiramberro, Lindberg, Isometsa, Kahkonen, & Appelberg, 2013; Cullen et al., 2016; Hu et al., 2011), which we excluded in the present review.

*Clinical practice guidance*

      Based on the studies reviewed here, it appears that the most common rTMS treatment protocol associated with a reduction in depression symptoms is that of high frequency (10

Hz) rTMS, using 120% MT at a 4 second train and 26 second interval. Establishing the optimal number of rTMS sessions that are needed to provide the maximum amount of gains (i.e., reduced depression symptoms alongside minimum side effects) remains a top clinical priority. Based on these reviewed studies, it appears that approximately 30 sessions of rTMS (over 6–8 weeks) treatment can lead to a significant reduction in depression scores post-treatment compared to baseline, and in some cases, these improvements were reported to be maintained up to six-months post rTMS. However, more recent studies have reported treatment gains after only 10 sessions of rTMS over two weeks (including theta-burst) (Dhami et al., 2019; Zhang et al., 2019), and between 14–18 rTMS sessions over 2–6 weeks (Bloch et al., 2008; MacMaster et al., 2019; Rosenich et al., 2019; Yang et al., 2014). Further, it appears that rTMS may serve to also improve other symptoms linked to depression, such as sleep disturbances (i.e., hypersomnia) (Sonmez et al., 2019). Future, larger sampled rTMS trials should seek to investigate the sleep effects of rTMS in young people.

*Strengths and Limitations*

All of the reviewed studies included clinical samples of adolescents with depression. Importantly, all participants' clinical diagnoses were verified at baseline with validated measures. A second strength is that all studies excluded participants who had a history of other psychiatric and neurological disorders. Third, participants with co-morbid diagnoses were included. This is a strength given that young people seeking treatment for depression are likely to hold comorbid diagnoses (Cummings, Caporino, & Kendall, 2014).

Collectively, limitations are still present among the reviewed studies. For instance, they often have small sample sizes (N = 6–42), fail to control for the effects of ongoing alternative therapies (e.g., medication/psychotherapy treatments) and none included a sham-controlled condition, making it difficult to assess whether the reported reduction of

depression symptoms is due to the effects of rTMS alone. In all 14 studies, rTMS is delivered to the L-DLPFC (with 2 studies also administering stimulation to the R-DLPFC). Whilst still somewhat unclear, preliminary mechanistic evidence suggests that administering rTMS to the DLPFC normalises dysfunctional fronto-limbic networks in depression, (Liston et al., 2014); neural networks that continue to mature throughout adolescence (Lopez-Duran, Kovacs, & George, 2009). Whilst believed to be robust, irrespective of different scalp sites of stimulation (Health Quality Ontario, 2016), most studies reviewed here—particularly early studies—utilised the '5cm rule' for L-DLPFC localisation; which, based on the adult rTMS literature, may be an unreliable method (George et al., 2010; Mir-Moghtadaei et al., 2015). More recent studies have adopted the use of neuro-navigation techniques (e.g., MRI), which are considered to be a more accurate method, (e.g., Dunlop et al., 2015), either alongside or instead of the '5cm Rule' which is likely to improve the accuracy of treatment delivery.

Not all studies consistently assessed depression symptoms throughout the trial at regular intervals, and instead only collected assessments at baseline and post-treatment. While there are advantages to this (i.e., reduced participant burden), without regular assessment intervals it is unclear at what point treatment gains, if any, were achieved. For instance, in a 6-week trial, it could be that the most treatment gains (i.e., maximum decrease in depression symptoms) were obtained after 3 weeks of rTMS (e.g., 15 sessions), and then symptom reduction plateaued. With regular assessment throughout the trial, these effects could be captured and help inform future treatment guidelines for the use of rTMS as a treatment for depression in young people. Lastly, it is likely that reporting biases (e.g., publication bias, reporting bias) is at play within these studies as there are no RCTs and all the pre-post intervention studies report some beneficial effect on the reduction of symptoms.

*Recommendations for Future Research and Clinical Implications:*

In sum, there is a strong need to conduct sham-controlled randomized studies that assess the efficacy of rTMS in young people with depression, and our review reveals that there are a number of ongoing trials, mostly being conducted in the US. Although the studies reviewed here demonstrate promising evidence for the efficacy of rTMS, it is unclear without the addition of a sham control whether these improvements are due to rTMS alone or some placebo effect. It is also noteworthy that 3 of the trials registered on ClinicalTrials.gov (2 of which were RCTs) have been stopped prematurely.

Further, most studies focus on TRD, with little research surrounding the efficacy of rTMS in those with depressive disorders that have not failed prior anti-depressant treatments. This is important in order to be able to understand the place of rTMS in the treatment pathway of adolescents with depression, that is whether it should be offered as a choice (if effective) first line for depression, or whether it is best reserved for more difficult to treat cases. It is possible that young people with depression who are treatment resistant may differ in their response to rTMS compared to the population which is treatment naive. Future research should seek to conduct more multi-subject trials in young people with other forms of non TRD. These findings would have important clinical implications, one being that rTMS could be offered as a first-line treatment option for young people with major depression.

Lastly, the literature surrounding rTMS tends to focus on traditional forms of rTMS, neglecting more recent developments such as TBS. TBS offers some advantages over high-frequency rTMS protocols; because theta-burst stimulation can be achieved in a much shorter timeframe compared to traditional rTMS protocols, this would mean that patients would not have to endure long treatment sessions (e.g., 30 minutes) and may possibly need fewer sessions overall. This could also change the risk benefit ratio of the intervention via improving acceptability and modify its place in the treatment pathway. However, further research is needed to establish the efficacy of theta-burst protocols among young people with

depression. Indeed, an interesting avenue for future research would be a study comparing traditional rTMS to TBS in adolescent depression.

**Conclusion**

There is now an emerging body of research investigating the use of rTMS interventions to adolescent depression. Whilst limited by less than ideal study designs, the evidence is promising, and suggests that rTMS interventions may successfully reduce depression symptoms. However, further research is warranted, in particular a demand for sham-controlled randomised trials to better determine the efficacy of rTMS in treating adolescent depression needs to be met.

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**Appendix A: Supplementary Material**

The following material accompanies the article: *Repetitive Transcranial Magnetic stimulation (rTMS) for the Treatment of Depression in Adolescence: A Systematic Review.*
Authors: Danielle Hett, Jack Rogers, Clara Humpston, Steven Marwaha. **Corresponding author:** Danielle Hett. Email: d.hett@bham.ac.uk

This file includes:

*The Newcastle-Ottowa Scale (NOS) used to rate the risk of bias for each included study*

| Domain of bias | Criteria |
|---|---|
| **Selection** | |
| 1. Representativeness of the exposed cohort | a) truly representative of the average **depressed adolescent** * |
| | b) somewhat representative of the average **depressed adolescent** * |
| | c) selected groups of users (e.g., nurses, volunteers) |
| | d) no description of the derivation of the depressed adolescent cohort |
| 2. Selection of the non-exposed cohort **(i.e., comparator group)** | a) Drawn from the same community as the exposed cohort* |
| | b) Drawn from a different source |
| | c) No description of the derivation of the non-exposed cohort / **non exposed cohort not present in the study** |
| 3. Ascertainment of **depression** | a) Secure record (e.g., medical record) * |
| | b) Structured interview * |
| | c) Written self-report |
| | d) No description |
| 4. Demonstration that outcome of interest was not present at the start of the study | a) Yes * |
| | b) No |
| **Comparability** | |
| 1. Comparability of cohorts on the basis of the design or analysis | a) Study controls for **family history of depression and/or history of psychological stress** * |
| | b) Study controls for any additional factors **(e.g., sex, age, psychiatric diagnosis, baseline depression scores, adherence to intervention)** * |
| **Outcome** | |
| 1. Assessment of **depression symptoms** | a) Independent blind assessment * |
| | b) Record linkage * |
| | c) Self-report / clinician rated non-blind |
| | d) No description |
| 2. Was follow-up long enough for outcome to occur **(≥ 1 week post rTMS)** | a) Yes * |
| | b) No |

| | |
|---|---|
| 3. Adequacy of follow-up cohorts | a) Complete follow-up (all patients accounted for) * |
| | b) Subjects lost unlikely to introduce bias (**< 20%**) * |
| | c) Follow-up rate **< 80%** and no description of those lost |
| | d) No statement |

*Note.* * *represents one point being awarded. Text in bold highlights where authors have added in information needed to help rate the studies of this review.*

*Supplementary Material Table 2*
*The Newcastle-Ottowa Scale (NOS) risk of bias summary assessment of the included studies (N = 14)*

| | | Bloch et al. 2008 | Croarkin et al. 2012 | Croarkin et al. 2016 | Croarkin et al. 2018 | Dhami et al. 2018 | MacMaster et al. 2019 | Mayer et al. 2012 | Rosenich et al. 2018 | Sonmez et al. 2019 | Wall et al. 2011 | Wall et al. 2013 | Wall et al. 2016 | Yang et al. 2014 | Zhang et al. 2019 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Selection** | 1) Representativeness of the exposed cohort | B* | B* | B* | B* | B* | B* | B* | B* | B* | B* | B* | B* | B* | B* |
| | 2) Selection of the non-exposed cohort (e.g., comparator group) | C | C | C | C | C | C | C | C | C | C | C | C | C | C |
| | 3) Ascertainment of depression | B* | B* | B* | B* | B* | B* | B* | B* | B* | B* | B* | B* | B* | B* |
| | 4) Demonstration that outcome of interest was not present at the start of the study | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Comparability** | 1) Comparability of cohorts on the basis of the design or analysis | B* | A* | A* | A* | A* | B* | B* | B* | A* | A* | A* | A* | B* | B* |
| **Outcome** | 1) Assessment of depression symptoms | C | C | C | C | C | C | C | C | C | C | C | C | C | C |
| | 2) Was follow-up long enough for outcomes to occur | A* | A* | A* | A* | A* | A* | A* | A* | A* | A* | A* | A* | A* | A* |
| | 3) Adequacy of follow up of cohorts | A* | B* | A* | B* | B* | B* | B* | A* | B* | A* | C | C | C | C |
| | **Total number of stars** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 4 | 4 | 4 | 4 |
| | **Quality rating in line with guidance\*** | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Poor | Poor | Poor | Poor |

* Good quality: 3 or 4 stars in Selection domain AND 1 or 2 stars in Comparability domain AND 2 or 3 stars in Outcome domain Fair quality: 2 stars in Selection domain AND 1 or 2 stars in Comparability domain AND 2 or 3 stars in Outcome domain Poor quality: 0 or 1 star in Selection domain OR 0 stars in Comparability domain OR 0 or 1 stars in Outcome domain

| Database | Search terms (MeSH/Emtree) |
|---|---|
| PubMed | ("repetitive transcranial magnetic stimulation"[All Fields] OR ("transcranial magnetic stimulation"[MeSH Terms] OR ("transcranial"[All Fields] AND "magnetic"[All Fields] AND "stimulation"[All Fields]) OR "transcranial magnetic stimulation"[All Fields] OR "rtms"[All Fields]) OR ("Symp Theory Model Simul"[Journal] OR "tms"[All Fields])) AND (("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields]) OR "depressive disorder"[All Fields] OR "depression"[All Fields] OR "depression"[MeSH Terms]) OR (("emotions"[MeSH Terms] OR "emotions"[All Fields] OR "emotional"[All Fields]) AND ("disease"[MeSH Terms] OR "disease" |

| | # ▲ | Searches | Results | Type | Actions | Annotations | |
|---|---|---|---|---|---|---|---|
| ☐ | 1 | ▶ repetitive transcranial magnetic stimulation.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh] | 9924 | Advanced | Display Results \| More ▼ | 💬 | ⏏ Contrac |
| ☐ | 2 | ▶ rTMS.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh] | 10208 | Advanced | Display Results \| More ▼ | 💬 | |
| ☐ | 3 | ▶ TMS.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh] | 23163 | Advanced | Display Results \| More ▼ | 💬 | |
| ☐ | 4 | ▶ 1 or 2 or 3 | 31750 | Advanced | Display Results \| More ▼ | 💬 | |
| ☐ | 5 | ▶ depress*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh] | 1127167 | Advanced | Display Results \| More ▼ | 💬 | |
| ☐ | 6 | ▶ emotional disorder.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh] | 16802 | Advanced | Display Results \| More ▼ | 💬 | |
| ☐ | 7 | ▶ 5 or 6 | 1137893 | Advanced | Display Results \| More ▼ | 💬 | |
| ☐ | 8 | ▶ adolescen*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh] | 2032154 | Advanced | Display Results \| More ▼ | 💬 | |
| ☐ | 9 | ▶ child*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh] | 3363722 | Advanced | Display Results \| More ▼ | 💬 | |
| ☐ | 10 | ▶ young.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh] | 1103192 | Advanced | Display Results \| More ▼ | 💬 | |
| ☐ | 11 | ▶ teen*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh] | 64045 | Advanced | Display Results \| More ▼ | 💬 | |
| ☐ | 12 | ▶ 8 or 9 or 10 or 11 | 4966699 | Advanced | Display Results \| More ▼ | 💬 | |
| ☐ | 13 | ▶ 4 and 7 and 12 | 617 | Advanced | Display Results \| More ▼ | 💬 | |
| ☐ | 14 | ▶ limit 13 to english language | 600 | Advanced | Display Results \| More ▼ | 💬 | |
| ☐ | 15 | ▶ limit 14 to human | 580 | Advanced | Display Results \| More ▼ | 💬 | |
| ☐ | 16 | ▶ limit 15 to yr="2000 -Current" | 574 | Advanced | Display Results \| More ▼ | 💬 | |

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Supplementary Material Figure 1. Embase and PsycINFO Search Strategy

**Tables**

*Table 1*
*Study characteristics of included studies (N = 14) assessing rTMS in adolescent depression*

| Study | Location | Sample Size N | Age | rTMS location | Number of rTMS sessions | rTMS Frequency (Hz) | rTMS Protocol (sec per train/number of trains, sec per interval) | rTMS MT (%) | Depression Outcome Measure(s) | Baseline Depression Scores M | Post rTMS Depression /Follow-up Scores M |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Open-label trials (N = 8)*** | | | | | | | | | | | |
| Dhami et al. (2019) | Canada | 20 | M = 20.90 SD = 2.60 R = 16–24 | L-DLPFC R-DLPFC | 10 (2–2.5) | 1800 TBS | 1800 iTBS pulses to L-DLPFC followed by 1800, cTBS pulses to R-DLPFC | 80 | HAM-D | 22.40 (2.90) | 13.50 (5.00) |
| Zhang et al. (2019) | China | 42 | M = 14.60 SD = 2.00 R = 10–17 | L-DLPFC | 20 (unclear) | High (10) | (80 trains, 12) | 120 | HAM-D | 16.40 (5.10) | 4.30 (2.10) |

| Study | Country | N | Age | Site | Sessions | Frequency | Intensity/Duration | Pulses | Measure | Baseline | Post |
|---|---|---|---|---|---|---|---|---|---|---|---|
| MacMaster et al. (2019) | Canada | 32 | M =17.57<br>SD = 1.98<br>R = 13–21 | L-DLPFC | 15 | High (10) | (4, 26) | 120 | HAM-D | 20.25 (6.37) | 9.38 (5.44) |
| *Study assessed three separate rTMS protocols: 2 unilateral and 1 bilateral treatment* | | | | | | | | | | | |
| Rosenich et al. (2019) | Australia | 15 | M = 20.69<br>SD = 2.55<br>R = 17–25 | R-DLPFC<br>L-DLPFC | 18<br>(6) | *Unilateral:*<br>Low (1)<br>*Bilateral:*<br>High (10) +<br>Low (1) | *Unilateral:*<br>either 15 mins or 30 mins of Low<br>*Bilateral:*<br>15 mins of High (10)<br>+<br>15 mins of Low (1) | 110 | HAM-D | 19.20 (5.16) | 11.93 (6.22) |
| Croarkin et al. (2016) | USA | 10 | M = 15.40<br>SD = 1.20<br>R = 13–17 | L-DLPFC | 30<br>(6-8) | High (10) | (4, 26) | 120 | CDRS-R | 62.90 (8.20) | 41.80 (13.20) |
| Yang et al. (2014) | Canada | 6 | M =18.70<br>SD = 1.95<br>R = 15–21 | L-DLPFC | 15 | High (10) | (4, 26) | 120 | HAM-D | 30.50 (5.45) | 9.80 (1.26) |

| Study | Country | N | Age | Site | Frequency | Intensity | | Pulses | Scale | Baseline | Post |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Wall et al. (2011) | USA | 8 | M = 16.54 SD = 1.18 R = 14.60–17.80 | L-DLPFC | 30 (6-8) | High (10) | (4, 26) | 120 | CDRS-R | 65.90 (6.60) | 36.20 (8.30) |
| Bloch et al. (2008) | Israel | 9 | M = 17.30 SD = 0.62 R = 16–18 | L-DLPFC | 14 (2) | High (10) | (2, 58) | 80 | CDRS-R | 71.78 (6.26) | 55.11 (14.79) |

***Post-hoc data analysis studies/ follow-up studies (N = 6)***

| Study | Country | N | Age | Site | Frequency | Intensity | | Pulses | Scale | Baseline | Post |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Sonmez et al. (2019)[a] | USA | 17 | M = 15.94 SD = 1.35 R = 13–19 | L-DLPFC | 30 (6-8) | High (10) | (40 pulse trains, 26) | 120 | CDRS-R | 67.51 (8.16) | 38.94 (13.61) |
| Croarkin et al. (2018)[b] | USA | 19 | M = 16.00 SD = 1.29 R = 13–19 | L-DLPFC | 30 (6-8) | High (10) | (4, 26) | 120 | CDRS-R (*suicidal ideation item*) | 2.52 (1.57) | 1.44 (1.15) |
| Wall et al. (2016)[c] | USA | 10 | M = 15.90 SD = 1.10 R = 13.90–17.40 | L-DLPFC | 30 (6-8) | High (10) | (4, 26) | 120 | CDRS-R | 62.90 (8.20) | 41.80 (13.20) |

| Study | Country | N | Age | Stimulation site | Sessions | Intensity | | Pulses | Scale | Baseline | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Wall et al. (2013)[d] | USA | 18 | M = 16.20 SD = 1.10 R = 13.90–17.80 | L-DLPFC | 30 (6-8) | High (10) | (4, 26) | 120 | CDRS-R | 64.73 (7.48) | 13.71 (11.95) |
| Croarkin et al. (2012)[e] | USA | 7 | M = 16.14 SD = 1.12 R = 14–17 | L-DLPFC | 30 (6-8) | High (10) | (4, 26) | 120 | CDRS-R | 65.14 (7.76) | 31.86 (6.74) |
| Mayer et al. (2012) (3-year follow-up study)[f] | Israel | 8 (lost 1 at follow-up) | M = 20.40 SD = unknown R = 19–22 | L-DLPFC | 14 (2) | High (10) | (2, 58) | 80 | CDRS-R | 71.78 (6.26) | 3-year Follow up scores not reported |

*Note:* L-DLPFC = left dorsolateral prefrontal cortex; R-DLPFC = right dorsolateral prefrontal cortex; iTBS = intermittent theta-burst stimulation; cTBS = continuous theta-burst stimulation; HAM-D = Hamilton Rating Scale for Depression; CDRS-R = Children's Depression Rating Scale Revised; M = mean; SD = standard deviation; R = range

[a] Data pooled from Wall 2016/ Wall 2013/ Wall 2011

[b] Data pooled from Wall 2011/ Wall 2016

[c] Same dataset as Croarkin 2016

[d] Pooled dataset from Croarkin 2016/ Wall 2011

[e] Post hoc analysis of Wall 2011

[f] 3-year follow up study based on participants from Bloch 2008

*Table 2*
*Summary of reported side effects from the open-trial rTMS studies (N = 8)*

| | Headache | Tiredness | Scalp Pain | Musculoskeletal | Discomfort | Neck Pain | Light headedness | Chest tightness | Nausea | Anxiety | Unpleasant tingling | Suicidal Ideation (post-rTMS) | None reported | Information on the frequency of reported side effects |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dhami et al. (2019) | X | | X | | | | | X | X | X | | X | | • 9/17 patients reported some form of suicidal ideation post-rTMS<br>• Headaches were reported at least once by 13 patients |
| Zhang et al. (2019) | X | | | | X | | | | | | | | | • 2/42 reported headache/musculoskeletal discomfort |
| MacMaster et al. (2019) | X | | | | | X | X | | X | | X | | | • 10/32 reported mild to moderate headaches and 7/32 reported mild neck pain |

| Study | | | | | Side effects |
|---|---|---|---|---|---|
| Rosenich et al. (2019) | X | X | X | | • Does not report frequency of reported side effects |
| Croarkin et al. (2016) | | | | X | • No side effects reported |
| Yang et al. (2014) | X | | X | | • Does not report frequency of reported side effects |
| Wall et al. (2011) | | | X | | • 1 adolescent discontinued treatment after 5 minutes of treatment due to scalp discomfort (and no longer included in the analysis)<br>• 3/8 reported scalp discomfort |
| Bloch et al. (2008) | X | | | | • 5/9 reported mild headache |

**Figure Captions**

Figure 1. Systematic review process: PRISMA diagram

| Records identified through searching databases: PubMed, Embase, PsychINFO, Web of Science and CENTRAL: (n = 1911) | Additional records identified through other sources: |
|---|---|
| | - Hand-searching the four previous rTMS review papers (n = 0) |
| | - Searching ClinicalTrials.gov (n = 16) |
| | - Contacting experts in the field (n = 0) |
| | - Google scholar (first 30 pages) (n = 0) |
| | - Hand-searching the last two years of three separate journals (n = 0) |

**Records after duplicates (n = 785) removed**

(n = 1142)

**Records screened at title/abstract stage** (n = 1142)

→ **Excluded (n = 1094)**
Not relevant, review papers, meta-analyses, adult populations, did not use rTMS but other forms of TMS

**Records (including clinical trials/conference proceedings abstracts) screened at full-text stage (n = 69)**

→ **Excluded Records (n = 46)**
- Case studies (n = 11)
- Studies that did not use an rTMS protocol or adolescent samples (n = 23)
- Conference abstracts removed as data reported in the abstracts is from an included paper (n = 4)
- Clinicaltrials.gov: Terminated trials/trial protocols which are already included in the published articles (n =8)

**Studies included in the systematic review:**
14 published studies

**Other current studies mentioned in the review:**
1 Conference abstract (unpublished research article)
8 current ongoing clinical trials registered