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Hett, Danielle; Rogers, Jack; Humpston, Clara; Marwaha, Steven

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

Danielle Hett[1,2]

Jack Rogers[1]

Clara Humpston[1]

Steven Marwaha[1,2]

[1]Institute for Mental Health, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK.

[2]National Centre for Mental Health, The Barberry, 25 Vincent Drive, Birmingham and Solihull Mental Health Trust, Birmingham, UK

Corresponding author: Corresponding author: Danielle Hett, Institute for Mental Health, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK.

Email: D.Hett@bham.ac.uk

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

(Downar 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 (ps $= .053 - .209$). 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.

References

APA, A. P. A. (2000). Diagnostic and statisitcal manual of mental disorders (4th edn, text
revision). *Washington, DC.*

Bardone, A. M., Moffitt, T. E., Caspi, A., Dickson, N., Stanton, W. R., & Silva, P. A. (1998).
Adult physical health outcomes of adolescent girls with conduct disorder, depression,
and anxiety. *Journal of the American Academy of Child and Adolescent Psychiatry,
37*(6), 594-601. doi:10.1097/00004583-199806000-00009

Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-invasive magnetic stimulation of
human motor cortex. *Lancet, 1*(8437), 1106-1107. doi:10.1016/s0140-
6736(85)92413-4

Berlim, M. T., Van den Eynde, F., & Jeff Daskalakis, Z. (2013). Clinically meaningful
efficacy and acceptability of low-frequency repetitive transcranial magnetic
stimulation (rTMS) for treating primary major depression: a meta-analysis of
randomized, double-blind and sham-controlled trials. *Neuropsychopharmacology,
38*(4), 543-551. doi:10.1038/npp.2012.237

Bernstein, I. H., Rush, A. J., Trivedi, M. H., Hughes, C. W., Macleod, L., Witte, B. P., . . .
Emslie, G. J. (2010). Psychometric properties of the Quick Inventory of Depressive
Symptomatology in adolescents. *International Journal of Methods in Psychiatric
Research, 19*(4), 185-194. doi:10.1002/mpr.321

Bloch, Y., Grisaru, N., Harel, E. V., Beitler, G., Faivel, N., Ratzoni, G., . . . Levkovitz, Y.
(2008). Repetitive transcranial magnetic stimulation in the treatment of depression in
adolescents: an open-label study. *Journal of ECT, 24*(2), 156-159.
doi:10.1097/YCT.0b013e318156aa49

Bromet, E., Andrade, L. H., Hwang, I., Sampson, N. A., Alonso, J., de Girolamo, G., . . .

Kessler, R. C. (2011). Cross-national epidemiology of DSM-IV major depressive

episode. *BMC Medicine, 9*(1), 90. doi:10.1186/1741-7015-9-90

Chiramberro, M., Lindberg, N., Isometsa, E., Kahkonen, S., & Appelberg, B. (2013).

Repetitive transcranial magnetic stimulation induced seizures in an adolescent patient

with major depression: a case report. *Brain Stimululation, 6*(5), 830-831.

doi:10.1016/j.brs.2013.02.003

Cipriani, A., Zhou, X., Del Giovane, C., Hetrick, S. E., Qin, B., Whittington, C., . . . Xie, P.

(2016). Comparative efficacy and tolerability of antidepressants for major depressive

disorder in children and adolescents: a network meta-analysis. *Lancet, 388*(10047),

881-890. doi:10.1016/S0140-6736(16)30385-3

Copeland, W. E., Shanahan, L., Costello, E. J., & Angold, A. (2009). Childhood and

adolescent psychiatric disorders as predictors of young adult disorders. *Archives of

General Psychiatry, 66*(7), 764-772. doi:10.1001/archgenpsychiatry.2009.85

Costello, E., Erkanli, A., & Angold, A. (2006). Is there an epidemic of child or adolescent

depression? *Journal of Child Psychology and Psychiatry, 47*(12), 1263-1271.

doi:10.1111/j.1469-7610.2006.01682.x

Croarkin, P. E., & MacMaster, F. P. (2019). Transcranial Magnetic Stimulation for

Adolescent Depression. *Child and Adolescent Psychiatric Clinics of North America,

28*(1), 33-43. doi:10.1016/j.chc.2018.07.003

Croarkin, P. E., Nakonezny, P. A., Deng, Z. D., Romanowicz, M., Voort, J. L. V., Camsari,

D. D., . . . Lewis, C. P. (2018). High-frequency repetitive TMS for suicidal ideation in

adolescents with depression. *Journal of Affective Disorders, 239*, 282-290.

doi:10.1016/j.jad.2018.06.048

Croarkin, P. E., Nakonezny, P. A., Wall, C. A., Murphy, L. L., Sampson, S. M., Frye, M. A.,

    & Port, J. D. (2016). Transcranial magnetic stimulation potentiates glutamatergic

    neurotransmission in depressed adolescents. *Psychiatry Research: Neuroimaging,*

    247, 25-33. doi:10.1016/j.pscychresns.2015.11.005

Croarkin, P. E., Wall, C. A., & Lee, J. (2011). Applications of transcranial magnetic

    stimulation (TMS) in child and adolescent psychiatry. *International Review of*

    Psychiatry, 23(5), 445-453. doi:10.3109/09540261.2011.623688

Croarkin, P. E., Wall, C. A., McClintock, S. M., Kozel, F. A., Husain, M. M., & Sampson, S.

    M. (2010). The emerging role for rTMS in optimizing the treatment of adolescent

    depression. *The Journal of ECT, 26*(4), 323. doi:10.1097/YCT.0b013e3181dd17eb

Croarkin, P. E., Wall, C. A., Nakonezny, P. A., Buyukdura, J. S., Husain, M. M., Sampson,

    S. M., . . . Kozel, F. A. (2012). Increased cortical excitability with prefrontal high-

    frequency repetitive transcranial magnetic stimulation in adolescents with treatment-

    resistant major depressive disorder. *Journal of Child and Adolescent*

    Psychopharmacology, 22(1), 56-64. doi:10.1089/cap.2011.0054

Cullen, K. R., Jasberg, S., Nelson, B., Klimes-Dougan, B., Lim, K. O., & Croarkin, P. E.

    (2016). Seizure Induced by Deep Transcranial Magnetic Stimulation in an Adolescent

    with Depression. *Journal of Child and Adolescent Psychopharmacology, 26*(7), 637-

    641. doi:10.1089/cap.2016.0070

Cummings, C. M., Caporino, N. E., & Kendall, P. C. (2014). Comorbidity of anxiety and

    depression in children and adolescents: 20 years after. *Psychological Bulletin, 140*(3),

    816-845. doi:10.1037/a0034733

D'Agati, D., Bloch, Y., Levkovitz, Y., & Reti, I. (2010). rTMS for adolescents: Safety and

    efficacy considerations. *Psychiatry Research, 177*(3), 280-285.

    doi:10.1016/j.psychres.2010.03.004

Delis, D. C., Kramer, J. H., Kaplan, E., & Holdnack, J. (2004). Reliability and validity of the Delis-Kaplan Executive Function System: an update. *Journal of the International Neuropsychological Society, 10*(2), 301-303. doi:10.1017/S1355617704102191

Dhami, P., Knyahnytska, Y., Atluri, S., Lee, J., Courtney, D. B., Croarkin, P. E., . . . Farzan, F. (2019). Feasibility and clinical effects of theta burst stimulation in youth with major depressive disorders: An open-label trial. *Journal of Affective Disorders, 258*, 66-73. doi:10.1016/j.jad.2019.07.084

Donaldson, A. E., Gordon, M. S., Melvin, G. A., Barton, D. A., & Fitzgerald, P. B. (2014). Addressing the needs of adolescents with treatment resistant depressive disorders: a systematic review of rTMS. *Brain Stimulation, 7*(1), 7-12. doi:10.1016/j.brs.2013.09.012

Downar, J., Geraci, J., Salomons, T. V., Dunlop, K., Wheeler, S., McAndrews, M. P., . . . Giacobbe, P. (2014). Anhedonia and reward-circuit connectivity distinguish nonresponders from responders to dorsomedial prefrontal repetitive transcranial magnetic stimulation in major depression. *Biological Psychiatry, 76*(3), 176-185. doi:10.1016/j.biopsych.2013.10.026

Dunlop, K., Gaprielian, P., Blumberger, D., Daskalakis, Z. J., Kennedy, S. H., Giacobbe, P., & Downar, J. (2015). MRI-guided dmPFC-rTMS as a treatment for treatment-resistant major depressive disorder. *Journal of Visualized Experiments*(102), e53129. doi:10.3791/53129

Ferguson, J. M. (2001). SSRI Antidepressant Medications: Adverse Effects and Tolerability. *Primare Care Companion Journal of Clinical Psychiatry, 3*(1), 22-27. doi:10.4088/pcc.v03n0105

Fergusson, D. M., Horwood, L. J., Ridder, E. M., & Beautrais, A. L. (2005). Subthreshold depression in adolescence and mental health outcomes in adulthood. *Archives General Psychiatry, 62*(1), 66-72. doi:10.1001/archpsyc.62.1.66

Fink, E., Patalay, P., Sharpe, H., Holley, S., Deighton, J., & Wolpert, M. (2015). Mental Health Difficulties in Early Adolescence: A Comparison of Two Cross-Sectional Studies in England From 2009 to 2014. *Journal of Adolescent Health, 56*(5), 502-507. doi:10.1016/j.jadohealth.2015.01.023

Fletcher, J. M. (2008). Adolescent depression: diagnosis, treatment, and educational attainment. *Health Economics, 17*(11), 1215-1235. doi:10.1002/hec.1319

Ganapathy, A., Adhikari, N. K., Spiegelman, J., & Scales, D. C. (2012). Routine chest x-rays in intensive care units: a systematic review and meta-analysis. *Critical Care, 16*(2), R68. doi:10.1186/cc11321

George, M. S., Lisanby, S. H., Avery, D., McDonald, W. M., Durkalski, V., Pavlicova, M., . . . Sackeim, H. A. (2010). Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Archives of General Psychiatry, 67*(5), 507-516. doi:10.1001/archgenpsychiatry.2010.46

George, M. S., Nahas, Z., Molloy, M., Speer, A. M., Oliver, N. C., Li, X. B., . . . Ballenger, J. C. (2000). A controlled trial of daily left prefrontal cortex TMS for treating depression. *Biological Psychiatry, 48*(10), 962-970. doi:10.1016/s0006-3223(00)01048-9

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry, 23*(1), 56-62. doi:10.1136/jnnp.23.1.56

Hasin, D. S., Sarvet, A. L., Meyers, J. L., Saha, T. D., Ruan, W. J., Stohl, M., & Grant, B. F. (2018). Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA psychiatry, 75*(4), 336-346.

Health Quality Ontario. (2016). Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis of randomized controlled trials. *Ontario Health Technology Assessment Series, 16*(5), 1.

Hetrick, S., Merry, S., McKenzie, J., Sindahl, P., & Proctor, M. (2007). Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. *Cochrane Database Systematic Review*(3), CD004851. doi:10.1002/14651858.CD004851.pub2

Higgins, J. P., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., & Welch, V. A. (2019). *Cochrane Handbook for Systematic Reviews of Interventions*: John Wiley & Sons.

Hu, S. H., Wang, S. S., Zhang, M. M., Wang, J. W., Hu, J. B., Huang, M. L., . . . Xu, Y. (2011). Repetitive transcranial magnetic stimulation-induced seizure of a patient with adolescent-onset depression: a case report and literature review. *Journal of International Medical Research, 39*(5), 2039-2044. doi:10.1177/147323001103900552

Iwabuchi, S. J., Peng, D., Fang, Y., Jiang, K., Liddle, E. B., Liddle, P. F., & Palaniyappan, L. (2014). Alterations in effective connectivity anchored on the insula in major depressive disorder. *European Neuropsychopharmacology, 24*(11), 1784-1792. doi:10.1016/j.euroneuro.2014.08.005

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., . . . Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*(7), 980-988. doi:10.1097/00004583-199707000-00021

Kim-Cohen, J., Caspi, A., Moffitt, T. E., Harrington, H., Milne, B. J., & Poulton, R. (2003). Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. *Archives of General Psychiatry, 60*(7), 709-717. doi:10.1001/archpsyc.60.7.709

Klein, J. B., Jacobs, R. H., & Reinecke, M. A. (2007). Cognitive-behavioral therapy for adolescent depression: a meta-analytic investigation of changes in effect-size estimates. *Journal of the American Academy of Child and Adolescent Psychiatry, 46*(11), 1403-1413. doi:10.1097/chi.0b013e3180592aaa

Klomjai, W., Katz, R., & Lackmy-Vallee, A. (2015). Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). *Annals of Physical and Rehabilitation Medicine, 58*(4), 208-213. doi:10.1016/j.rehab.2015.05.005

Kowalewski, K., McLennan, J. D., & McGrath, P. J. (2011). A preliminary investigation of wait times for child and adolescent mental health services in Canada. *Journal of the Canadian Academy of Child and Adolescent Psychiatry, 20*(2), 112-119. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21541100

Lee, J., Knyahnytska, Y., Dhami, P., Blumberger, D. M., Daskalakis, J., Courtney, D., . . . Farzan, F. (Unpublished). T135. Combination Theta-Burst Stimulation and Cognitive Training for Youth Depression. *Biological Psychiatry, 85*(10), S181.

Lewinsohn, P. M., Rohde, P., & Seeley, J. R. (1994). Psychosocial risk factors for future adolescent suicide attempts. *Journal of Consulting and Clinical Psychology, 62*(2), 297-305. doi:10.1037//0022-006x.62.2.297

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P., . . . Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Annals of Internal Medicine, 151*(4), W-65-W-94.

Liston, C., Chen, A. C., Zebley, B. D., Drysdale, A. T., Gordon, R., Leuchter, B., . . . Dubin, M. J. (2014). Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biological Psychiatry, 76*(7), 517-526. doi:10.1016/j.biopsych.2014.01.023

Lopez-Duran, N. L., Kovacs, M., & George, C. J. (2009). Hypothalamic-pituitary-adrenal axis dysregulation in depressed children and adolescents: a meta-analysis. *Psychoneuroendocrinology, 34*(9), 1272-1283. doi:10.1016/j.psyneuen.2009.03.016

Luciana, M. (2003). Practitioner review: computerized assessment of neuropsychological function in children: clinical and research applications of the Cambridge Neuropsychological Testing Automated Battery (CANTAB). *Journal of Child Psychology and Psychiatry, 44*(5), 649-663. doi:10.1111/1469-7610.00152

MacMaster, F. P., Croarkin, P. E., Wilkes, T. C., McLellan, Q., Langevin, L. M., Jaworska, N., . . . Kirton, A. (2019). Repetitive Transcranial Magnetic Stimulation in Youth With Treatment Resistant Major Depression. *Frontiers in Psychiatry, 10*, 170. doi:10.3389/fpsyt.2019.00170

Magavi, L. R., Reti, I. M., & Vasa, R. A. (2017). A review of repetitive transcranial magnetic stimulation for adolescents with treatment-resistant depression. *International Review of Psychiatry, 29*(2), 79-88. doi:10.1080/09540261.2017.1300574

Mayer, G., Aviram, S., Walter, G., Levkovitz, Y., & Bloch, Y. (2012). Long-term follow-up of adolescents with resistant depression treated with repetitive transcranial magnetic stimulation. *Journal of ECT, 28*(2), 84-86. doi:10.1097/YCT.0b013e318238f01a

Mir-Moghtadaei, A., Caballero, R., Fried, P., Fox, M. D., Lee, K., Giacobbe, P., . . . Downar, J. (2015). Concordance between BeamF3 and MRI-neuronavigated target sites for repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex. *Brain Stimulation, 8*(5), 965-973. doi:10.1016/j.brs.2015.05.008

NICE. (2015). Repetitive transcranial magnetic stimulation for depression. In: NICE London.

Nord, C. L., Halahakoon, D. C., Limbachya, T., Charpentier, C., Lally, N., Walsh, V., . . . Roiser, J. P. (2019). Neural predictors of treatment response to brain stimulation and psychological therapy in depression: a double-blind randomized controlled trial. *Neuropsychopharmacology, 44*(9), 1613-1622. doi:10.1038/s41386-019-0401-0

O'Reardon, J. P., Solvason, H. B., Janicak, P. G., Sampson, S., Isenberg, K. E., Nahas, Z., . . . Sackeim, H. A. (2007). Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biological Psychiatry, 62*(11), 1208-1216. doi:10.1016/j.biopsych.2007.01.018

Patalay, P., & Gage, S. H. (2019). Changes in millennial adolescent mental health and health-related behaviours over 10 years: a population cohort comparison study. *International Journal of Epidemiology, 48*(5), 1650-1664. doi:10.1093/ije/dyz006

Penn, E., & Tracy, D. K. (2012). The drugs don't work? antidepressants and the current and future pharmacological management of depression. *Therapeutic Advances in Psychopharmacology, 2*(5), 179-188. doi:10.1177/2045125312445469

Posner, K., Brown, G. K., Stanley, B., Brent, D. A., Yershova, K. V., Oquendo, M. A., . . . Mann, J. J. (2011). The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *The American Journal of Psychiatry, 168*(12), 1266-1277. doi:10.1176/appi.ajp.2011.10111704

Poznanski, E. O., Grossman, J. A., Buchsbaum, Y., Banegas, M., Freeman, L., & Gibbons, R. (1984). Preliminary studies of the reliability and validity of the children's depression rating scale. *Journal of the American Academy of Child and Adolescent Psychiatry, 23*(2), 191-197. doi:10.1097/00004583-198403000-00011

Ridding, M. C., & Rothwell, J. C. (2007). Is there a future for therapeutic use of transcranial

magnetic stimulation? *Nature Reviews Neuroscience, 8*(7), 559-567.

doi:10.1038/nrn2169.

Rosenich, E., Gill, S., Clarke, P., Paterson, T., Hahn, L., & Galletly, C. (2019). Does rTMS

reduce depressive symptoms in young people who have not responded to

antidepressants? *Early Intervention in Psychiatry, 13*(5), 1129-1135.

doi:0.1111/eip.12743

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., . . .

Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.):

the development and validation of a structured diagnostic psychiatric interview for

DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59 Suppl 20*(20), 22-33;quiz 34-

57. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9881538

Sonmez, A. I., Kucuker, M. U., Lewis, C. P., Kolla, B. P., Doruk Camsari, D., Vande Voort,

J. L., . . . Croarkin, P. E. (2019). Improvement in hypersomnia with high frequency

repetitive transcranial magnetic stimulation in depressed adolescents: Preliminary

evidence from an open-label study. *Progress in Neuro-Psychopharmacology &*

Biological Psychiatry, 97, 109763. doi:10.1016/j.pnpbp.2019.109763

Sunderajan, P., Gaynes, B. N., Wisniewski, S. R., Miyahara, S., Fava, M., Akingbala, F., . . .

Trivedi, M. H. (2010). Insomnia in patients with depression: a STAR*D report. *CNS*

Spectrums, 15(6), 394-404. doi:10.1017/s1092852900029266

Talley, J. (1993). Children's auditory verbal learning test. *Professional manual. Odessa, FL:*

Psychological Assessment Resources Inc.

Thapar, A., Collishaw, S., Pine, D. S., & Thapar, A. K. (2012). Depression in adolescence.

Lancet, 379(9820), 1056-1067. doi:10.1016/S0140-6736(11)60871-4

Twenge, J. M., Cooper, A. B., Joiner, T. E., Duffy, M. E., & Binau, S. G. (2019). Age, period, and cohort trends in mood disorder indicators and suicide-related outcomes in a nationally representative dataset, 2005–2017. *Journal of abnormal psychology, 128*(3), 185.

Vujeva, H. M., & Furman, W. (2011). Depressive symptoms and romantic relationship qualities from adolescence through emerging adulthood: A longitudinal examination of influences. *Journal of Clinical Child & Adolescent Psychology, 40*(1), 123-135. doi:10.1080/15374416.2011.533414

Wall, C. A., Croarkin, P. E., Maroney-Smith, M. J., Haugen, L. M., Baruth, J. M., Frye, M. A., . . . Port, J. D. (2016). Magnetic Resonance Imaging-Guided, Open-Label, High-Frequency Repetitive Transcranial Magnetic Stimulation for Adolescents with Major Depressive Disorder. *Journal of Child and Adolescent Psychopharmacology, 26*(7), 582-589. doi:10.1089/cap.2015.0217

Wall, C. A., Croarkin, P. E., McClintock, S. M., Murphy, L. L., Bandel, L. A., Sim, L. A., & Sampson, S. M. (2013). Neurocognitive effects of repetitive transcranial magnetic stimulation in adolescents with major depressive disorder. *Frontiers in Psychiatry, 4*, 165. doi:10.3389/fpsyt.2013.00165

Wall, C. A., Croarkin, P. E., Sim, L. A., Husain, M. M., Janicak, P. G., Kozel, F. A., . . . Sampson, S. M. (2011). Adjunctive use of repetitive transcranial magnetic stimulation in depressed adolescents: a prospective, open pilot study. *The Journal of Clinical Psychiatry, 72*(9), 1263-1269. doi:10.4088/JCP.11m07003.

Wells, G. A., Tugwell, P., O'Connell, D., Welch, V., Peterson, J., Shea, B., & Losos, M. (2014). *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses*. Ottawa Hospital Research Institute

World Health Organisation. (2019). Retrieved from https://www.who.int/news-room/fact-

    sheets/detail/adolescent-mental-

    health#:~:text=Globally%2C%20depression%20is%20the%20fourth,those%20aged%

    2010%E2%80%9314%20years.

Yang, X. R., Kirton, A., Wilkes, T. C., Pradhan, S., Liu, I., Jaworska, N., . . . MacMaster, F.

    P. (2014). Glutamate alterations associated with transcranial magnetic stimulation in

    youth depression: a case series. *Journal of ECT, 30*(3), 242-247.

    doi:10.1097/YCT.0000000000000094

Young Minds. (2018). New figures on CAMHS waiting times. Retrieved from

    https://youngminds.org.uk/blog/new-figures-on-camhs-waiting-times/

Zhang, T., Zhu, J., Xu, L., Tang, X., Cui, H., Wei, Y., . . . Liu, X. (2019). Add-on rTMS for

    the acute treatment of depressive symptoms is probably more effective in adolescents

    than in adults: evidence from real-world clinical practice. *Brain Stimulation, 12*(1),

    103-109. doi:10.1016/j.brs.2018.09.007

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 **<u>depressed adolescent</u>** * b) somewhat representative of the average **<u>depressed adolescent</u>** * 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

		1	2	3	4	5	6	7	8	9	10	11	12	13	14
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 ▾	☐
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 ▾	☐

Save   Remove   **Combine with:**   AND   OR   Deduplicate

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	Region	Sessions	Frequency	Intensity	Pulses	Scale	Baseline	Post
MacMaster et al. (2019)	Canada	32	M =17.57 SD = 1.98 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 SD = 2.55 R = 17–25	R-DLPFC L-DLPFC	18 (6)	*Unilateral:* Low (1) *Bilateral:* High (10) + Low (1)	*Unilateral:* either 15 mins or 30 mins of Low *Bilateral:* 15 mins of High (10) + 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 SD = 1.20 R = 13–17	L-DLPFC	30 (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 SD = 1.95 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		Intensity	Stimulation	Pulses	Measure	Baseline	Outcome
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		Intensity	Stimulation	Pulses	Measure	Baseline	Outcome
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)

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 • 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

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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) • 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