Transcranial Magnetic Stimulation (TMS) for the Treatment of Major Depressive Disorder: A Systematic Review

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***Abstract*—Major Depressive Disorder (MDD) is one of the major health problems commonly develop in adult years. Effective treatments typically include antidepressant medications, psychological therapies, complementary therapies, or a combination of several different methods. However, research into the effectiveness of Transcranial Magnetic stimulation (TMS) in treating MDD is limited. The current study aimed to perform a systematic review on the use of TMS for the treatment of MDD. This systematic review was conducted with randomized trials in which the effects of TMS compared with sham stimulation in adults who were diagnosed major depressive depression. Eighteen randomized controlled studies were included in this systematic review. The results across studies were relatively consistent, showing the high frequency rTMS was effective to treat MDD when applied to left dorsolateral prefrontal cortex (dlPFC), primary visual cortex, hand area of primary motor cortex, left dlPFC and dmPFC. Only four studies demonstrated that high frequency rTMS was ineffective to left dlPFC and both left and right dlPFC, and Theta Burst stimulation (TBS) to both left and right dlPFC was ineffective comparing with sham stimulation. The major limitations of the studies reviewed here are half of them didn't apply double-blinded design and only focus on adults which might cause bias. Therefore, more high-quality double-blinded trials and trials which focus on other groups of people are needed to evaluate the effects of TMS treatment precisely.**

***Index Terms*—Major depressive disorder (MDD), transcranial magnetic stimulation (TMS), systematic review, psychiatry.**

I. Introduction

Depression is one of the most common psychological disorders. According to Diagnostic and Statistical Manual of Mental Disorders (DSM-5),

the clinical symptoms of depression include significant distress, diminishing interest, and pleasure, impairment in social, occupational, or other important areas of functioning. According to a survey that conducted in 2015, approximately 322 million people which was 4.4% of the global population suffered from depression [1]. Furthermore, people in developing countries received less mental healthcare services than people in developed countries, and the proportion of the gross domestic product spent on health care was inclined to correspond to the percentage of people who received healthcare services [2]. The research showed that patients receiving less treatment were men, married people, less educated people, and people with the lowest or highest age, or income [2]. These results have proven that depression is a serious psychiatric disorder that causes lots of negative effects on individuals and society. The world should be aware that finding methods to treat depression should be one of the priorities now.

The causes of depression are complicated. Firstly, there are several social causes of depression, such as some severe stressful experiences and bullying. Stressful experiences like divorce, the death of a close relative or losing jobs are all the main causes of depression [3]. Bulling makes up a substantial percentage of cases of clinical depression. An investigation from 2015 demonstrated that 26.1% of depression is due to bullying [4]. Furthermore, some genetic factors also play an important role in leading to depression. The relatives of the probands who suffered from depression after stressful life events or chronic difficulties had a little bit higher lifetime prevalence than the relatives who were depressed without adversity. Furthermore, later studies found that depression may be associated with serotonin transporter polymorphism (5-HTTLPR) [5]. The frequency of s-alleles was higher in the MDD patients than that in healthy control [6]. However, there are some inconsistent results. For example, Risch et al. found that there is no association between depression and 5-HTTLPR [7]. Antidepressants (ADP) and cognitive therapy are usually used to treat depression. Selective serotonin reuptake inhibitor (SSRI), is a kind of antidepressant, which is used to improve 'serotonin imbalance' or 'serotonin deficiency' in the brain. A meta-analysis of data from 35 clinical trials indicates that drugs relieve depression when the severity of depression is high [8]. However, 30% or more of the patients cannot benefit from antidepressants and the process of treatment takes a long time to be effective [9]. Cognitive therapy is to treat depression by pointing out patients' negative thoughts and help patients to learn alternative ways to approach their experiences [10]. Nevertheless, one noticeable disadvantage of cognitive therapy is that it is not available for every patient because of its expensiveness [11].

Transcranial magnetic stimulation (TMS) which is a non-invasive brain stimulation method has been used in treating depression for the recent 20 years. The principle of TMS is that the magnetic field is generated by a magnetic flux line that passes vertically through the plane of the magnetic coil, usually tangent to the scalp [12]. The electric field is generated perpendicular to the magnetic field and the voltage of the electric field will induce currents that are parallel to the plane of the coil [13], causing depolarization, excitation, or inhibition of different types of neurons [14]. In

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general, low-frequency repetitive TMS (rTMS, < 1 Hz) is used to inhibit brain excitability and high-frequency rTMS (> 1 Hz) is considered to facilitate cortical excitability [15], depending on which brain area TMS is applied to. Nowadays, rTMS which is one of the methods to treat depression develops rapidly and gains popularity. An increasing number of studies indicate that rTMS can be monotherapy or the adjuvant treatment of pharmacotherapy [16]. Comparing with other kinds of treatments like electroconvulsive therapy (ECT), rTMS has fewer side effects and is more cost-effective [17].

II. Method

A. Literature Review

A search was conducted papers in PubMed/MEDLINE. We looked for articles published from January 2010 to December 2020. The following key terms were used: ("major depressive disorder" OR "MDD") AND ("transcranial magnetic stimulation" OR "TMS").

B. Eligibility Criteria

The included studies had to:(a)be written in English;(b) be human study;(c)be a journal article and have access to full text;(d)main focus on Major depressive disorder;(e)be not a review;(f)be not a case study;(h)only perform TMS or rTMS for treatment;(g)only involve adult participants;(h)have experimental data

C. Quality Assessment

A study with relatively good quality should have (Page et al., 2021): a) a control group -the method used for compare results of experiments; b) randomization -subjects are selected randomly and assigned randomly to different groups; c) blindness -subjects or researchers were blinded to the allocation of groups; d) sample selection -objects must be clinically diagnosed as the major depressive disorder; e)ethics approvement.

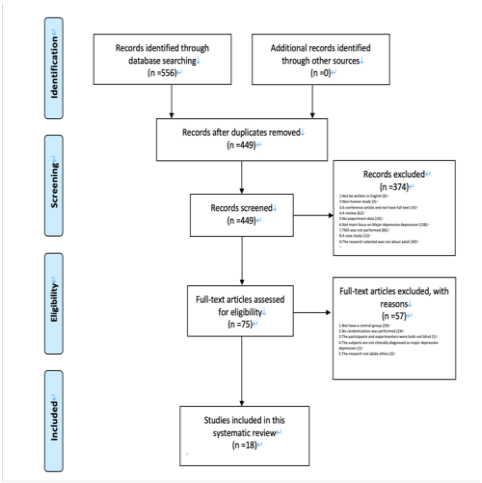

Fig. 1. PRISMA. the flow diagram of papers included and excluded.

III. Results

Eighteen studies were included in the current systematic review.

A. TMS over Left Dorsolateral Prefrontal Cortex (dlPFC)

There were nine studies that applied TMS to the left dorsolateral prefrontal cortex (dlPFC). More specifically, Chen *et al.* conducted a randomized and single-blinded trial, all patients were randomly selected to the rTMS group (n = 20) and the sham group (n = 20). The 10 Hz rTMS was applied every weekday for 4 weeks and each train lasted for 4 seconds over 40 trains. Moreover, the change in Hamilton Depression Scale (HAMD) has a positive correlation with the change in functional connectivity between the left insula and left amygdala in the TMS group ($p < 0.001$). However, such correlation changes before and after rTMS were not observed under sham condition ($p > 0.05$) [18]. These results suggested that 10 Hz rTMS which applied to dlPFC was effective in treating MDD.

1st author(year),country	Mean age	Diagnostic system	Design(number of subjects)	TMS treatment frequency(isi)-each session duration, total period)	Where the TMS applied	Outcome measure
Jin(2014),United States,China	42.50±15.60 46.30±12.70	DSM IV, HAMD- 17	Active rTMS(29), SHAM(16)	Fixed frequency ISI = 0.1 SI, random frequencies between 8.0-13.0 Hz(50min,4	the midline cortical surface	HAMD-17
Zhang(2021),China	31.54±11.59 31.67±12.77	SCID-I,HAMD- 24	Individualized group (24),Standard group (27),Sham group(23),Healthy controls(30),med (TMS before MDD(20),after MDD(20), sham rTMS MDD, before MDD(20), after MDD(20)	10Hz(20mins, 5days)	visual cortex	HAMD-24
Chen(2020),China	45.95±8.02 46.75±5.52 46.50±4.76	DSM-5,HAMD	MDD(20), sham rTMS MDD, before MDD(20), after MDD(20)	10Hz(25mins, 4 weeks)	left dorsolateral prefrontal cortex (dlPFC)	HRSD-17,HAMD-17
Filipčić(2019),Croatia	50.00 51.00 53.00	DSM-5	H1-coil (72),8-coil (75),Control (81)	10Hz(40mins, 4weeks)	left dorsolateral prefrontal cortex (dlPFC)	Hamilton depression rating scale (HAM-D17), odds ratio(OR)
Fitzgerald(2018),Australia	49.00±13.80 48.20±14.40	Mini International Neuropsychiatric Interview (MINI),Montgomery Asberg Depression Rating Scale (MADRS),2008(8-27)	Accelerated rTMS(58), standard rTMS(57)	10Hz(19.2s, 3weeks),10Hz(29.2s, 4weeks)	left dorsolateral prefrontal cortex (dlPFC)	MADRS, the Beck Depression Inventory BDI(II), the Scale of Suicidal Ideation (SSI), HDRS-17
Light(2019),United States	46.13±13.32 50.00±8.75	Montgomery-Asberg Depression Rating Scale - Clinician version (MADRS)	Active rTMS group (8), Sham group (11)	10Hz(20mins, 2 weeks)	left dorsolateral prefrontal cortex (dlPFC)	SHAPS,Empathic Happiness subscale
Luo(2018),Korea	35.86±12.51	DSM-IV	Active group (15), sham group(15)	10Hz(30mins, 15 weekdays)	5 cm anterior to the optimal surface site for activation of the right APB muscle over the dlPFC	17-item version of the Hamilton Rating Scale for Depression (HAM-D), 14-item version of the Hamilton Rating Scale for Anxiety (HAM-A), Beck Depression Inventory (BDI), The loudness dependence of auditory evoked potentials (LDAEP)
Carpenter(2017),United States	47.60±13.10 45.60±12.60	DSM-IV Axis I Disorder,HAMD-24,Columbia-Suicide Severity Rating Scale (C-SSRS),Antidepressant Treatment Response Questionnaire (ATRQ)	Active(30),sham(37)	10Hz(30s, 4-6 weeks)	left dorsolateral prefrontal cortex (dlPFC) and dorsomedial prefrontal cortex (dmPFC)	Clinical Global Impressions ratings for depressive illness severity (CGI-S),post-treatment CGI ratings for improvement in depression severity (CGI-I), Psychiatric diagnosis (SCID-CT), mental status exam (MMSE), evaluation of suicidality (C-SSRS), and CGI ratings characterizing depression severity and change over time,the Antidepressant Treatment Intake- ance Questionnaire (ATRQ)
Plewnia(2014),Germany,Rome	46.90±13.20 49.00±13.60	DSM-IV	cTBS(9), sham-stimulation (4)	50Hz Left-sided stimulation with iTBS(40s, 4-weeks), 50Hz Right-sided stimulation with cTBS(40s, 4 weeks)	left dorsolateral prefrontal cortex (dlPFC) and right dorsolateral prefrontal cortex (dlPFC)	Montgomery-Asberg Depression Rating Scale (MADRS),the Hamilton Depression Rating Scale (HAMD),the Beck Depression Inventory (BDI)
Prasser(2015),Germany	47.10±11.30	21-item Hamilton Rating Scale for Depression (HAMD)	(TMS to right dlPFC+ left dlPFC(1Hz,cTBS right dlPFC+iTDS left dlPFC(20),Theta-burst with Sham coil(18)	rTMS and cTBS to right dlPFC/1Hz(25s, 3 weeks),iTMS and iTBS to left dlPFC/ 10Hz(25s, 3 weeks)	left dorsolateral prefrontal cortex (dlPFC) and right dorsolateral prefrontal cortex (dlPFC)	21-item version of the Hamilton Depression Rating Scale (HAMD),Beck Depression Inventory (BDI), Clinical Global Impression scale (CGI), Global Assessment of Functioning scale (GAF)
Rosenquist(2013),United States	47.90±11.80 48.70±11.60	DSM-IV (SCID-IV),the Antidepressant Treatment History Form (ATHF)	Active (155) or sham (146)	10Hz(30s, 6 weeks)	left dorsolateral prefrontal cortex (dlPFC)	HAM-D,IDS-SR
van Eijndhoven(2020),Netherlands	40.60±11.10	DSM-IV (SCID)	real rTMS (15) ,sham rTMS (16)	10Hz(30mins, 4 weeks)	left dorsolateral prefrontal cortex (dlPFC)	HDRS-17
Vigneau(2015), France	44.60±10.70 42.30±9.40	Montgomery-Asberg Depression Rating Scale (MADRS)	healthy control (11), received cTBS(50), received iTBS(11)	50 Hz cTBS(40s,2 and 7days), 50Hz cTBS for iTBS paradigm(190s,2 and 7 days)	the left primary motor cortex	MADRS,State-Trait Anxiety Inventory questionnaire (STAI)
Wagdi(2016),United States	43	DSM-IV (SCID-IV), HAMD- 17	TMS(32), sham(31)	10Hz(15-30s, 3-4 weeks)	the point 5.0 cm anterior to the site of the motor cortex that maximally stimulated the right first dorsal interosseous muscle	HDRS
Valkonen-Korhonen(2018),Finland	57.10±11.10 56.40±11.30	the Hamilton depression rating scale (HAM-D),Montgomery-Asberg depression rating scale (MADRS),DSM-IV (SCID)	Active TMS(18), sham TMS(19)	10Hz(50mins, 6 weeks) 10 Hz(50mins, 6weeks)	left dorsolateral prefrontal cortex (dlPFC) and right dorsolateral prefrontal cortex (dlPFC)	HAM-D
Wang(2017),China	42.30±11.40 40.80±11.50 40.90±11.80	the International Classification of Diseases (10th version) (ICD-10), 17-item Hamilton Rating Scale for Depression (HAMD-17)	rTMS (91), rTMS +ADP(82)	10Hz(15mins, 3 months)	left dorsolateral prefrontal cortex(dlPFC)	HAMD-17, Clinical Global Impression-Severity (CGI-S) scale, YMRS, the Patient Inventory of Side Effects (PRISE)
Levkovitz(2015),United States	45.10±11.70 47.00±11.60	DSM-IV, Clinical Global Impression-Severity of Illness (CGI- S), 21-item Hamilton Depression Rating Scale (HDRS-21)	dTMS(101), sham(111)	10Hz(20mins,16 weeks)	left dorsolateral prefrontal cortex(dlPFC)	HDRS-21
Pan(2020),China	19.00±5.94, 21.40±5.91	DSM-IV, Mini-Neuropsychiatric Interview (MINI),24-item Hamilton Depression Rating Scale (HAMD-24), Beck Scale of Suicidal Ideation (BSI)	Active rTMS(21), sham rTMS(21)	10Hz(40mins,1 week)	BA46 (- 44, 40, and 2922) in the dlPFC	BSI, HAMD-24, Montgomery-Asberg Depression Rating Scale (MADRS), Wisconsin Card Sorting Test (WCST), Continuous Performance Test (CPT), 21 and Stroop Color-Word Test (SCWT)

Fig. 2. The information about papers included.

In another randomized controlled and single-blinded study, 228 patients were randomly allocated to H1-coil (n = 72), 8-coil (n = 75) or control group (n = 81). For the H1-coil group, patients received 18Hz rTMS and standard drug therapy for 20-min sessions over four weeks. For the 8-coil group, patients were treated with 10Hz rTMS and standard pharmacotherapy for 40-min sessions over four weeks. Patients in the control group only received standard pharmacotherapy. The results showed that the remission rate of patients in the H1-coil and 8-coil groups was greater in the control group. Moreover, Patients with severe MDD who have at least 17 scores in HAM-D17 during baseline (pre-treatment) evaluation in the H1-coil group had a significantly higher odds ratio for remission than the 8-coil group (CI95% 1.69–12.48; p = 0.003). The response rate of the H1-coil group was significantly better than that of the 8-coil (CI95% 1.04–5.21; p = 0.040) and the standard pharmacotherapy group (CI95% 3.29–26.26). The odds for response of 8-coil and control group were not significantly different (CI95% 0.87–5.06; p = 0.100). Additionally, there was a significant main effect of the treatment group in HAMD-17 scores. Post-hoc comparison showed that reduction of HAMD-17 score of H1-coil group was significantly higher compared with figure-8-coil group ($F_{1,132}$ = 3.97; p = 0.050; η^2 = 0.03) [19]. These results demonstrated that 18 Hz rTMS delivered by H1-coil group to dlPFC was

more effective than 10 Hz rTMS delivered by figure-to-8 coil group to left dlPFC, by showing remission and response rates in H1-coil group were both greater than figure-to-8 coil group and control group.

A randomized controlled trial involved 281 participants who were randomly assigned into three groups, including the rTMS +ADP (n = 82), rTMS (n = 91) and ADP group (n = 108). The duration of 10Hz rTMS was 15 minutes for 15 sessions in this 12-month study. The remission rate of MDD in rTMS-containing group was significantly lower compared with ADP group (15.9% and 24.2% vs. 44.4%, χ^2 = 20.165, d.f. = 2, p < 0.001). The difference of recurrence rate between rTMS +ADP and ADP group was 28.5% (χ^2 = 16.192, d.f. = 1, p = 0.001). The difference between rTMS and ADP group was 20.2% (χ^2 = 8.031, d.f. = 1, p = 0.005). However, no significant difference was found in recurrence rate of rTMS +ADP group and rTMS group (χ^2 = 1.371, d.f. = 1, p = 0.242) [20]. The results manifested that 10 Hz rTMS +ADP and 10 Hz rTMS treatment to left dlPFC were both effective compared with ADP treatment, but there was no significant difference in efficacy of 10Hz rTMS +ADP and 10Hz rTMS treatment.

A randomized controlled trial randomly assigned the participants to two groups including deep transcranial magnetic stimulation (dTMS) group (n = 89) and sham group (n = 92). Patients in the treatment group received 18Hz dTMS and each session lasted for 30 minutes over 4 weeks. The control group received sham treatment with the same parameters. The two groups were identical in terms of demographic parameters, clinical characteristics and Hamilton Depression Rating (HDRS-21) mean scores at baseline. At week 5, the response rates of dTMS and sham group were significantly different (chi-square test, p = 0.0138) which were 38.4% and 21.4% respectively, as well as the remission rates of dTMS and sham group were significantly different (chi- square test, p = 0.0051) which were 32.6% and 14.6% respectively. At week 16, there was a difference of 2.47 points in HDRS-21 between the active and sham groups, which was statistically different (p = 0.0259). The response rates of dTMS and sham group were significantly different (chi-squared test, p = 0.0086) which were 44.3% and 25.6%, whereas the remission rates of these two groups were not significantly different (p = 0.1492, chi-squared test) which was 31.8% and 21.2% respectively [21]. These results demonstrated that the 18Hz dTMS to left dlPFC was effective one week after the treatment and not effective at week 16.

A double-blinded, randomized and controlled study included 21 patients in the rTMS group and 21 patients in the sham group. The rTMS treatment was applied with a frequency of 10Hz for 120 trains of 20-second duration per session over 7 days. According to the results, the reduction of the Beck Scale of Suicidal Ideation (BSI) score of the active group was significantly greater than the sham group on the 3rd day (p < 0.001) and at the 7th day (p < 0.001). In addition, the reduction of HAMD score in the active group was significantly greater than the sham group (p < 0.001) after 7 consecutive days of treatment. The decline of Montgomery–Åsberg Depression Rating Scale (MADRS) score in the active group was significantly greater than the sham group as well after a week of treatment (p < 0.001) [22]. The results suggested that 10Hz rTMS to left dlPFC was effective to treat MDD comparing with sham stimulation.

A single-blinded, randomized controlled trial involved 115 patients in the treatment and analysis: 58 patients in the accelerated rTMS group and 57 patients in the standard group. In the accelerated group, patients received 10Hz rTMS which performed 4.2 seconds for each train over 3 days for 83, 83 and 84 trains respectively. In the standard rTMS group, 10Hz rTMS was performed 75 trains which lasted 29.2 seconds per train over 4 weeks. The results demonstrate that there was no significant difference between the groups in response rates and remission rates in any of the experimental analysis. Moreover, there was a significant main effect of time for MARS($F_{5, 489}$ = 24.415, p < 0.000), HDRS ($F_{1, 112}$ = 95.680, p < 0.000), Beck Depression Inventory-II(BDI) ($F_{5, 429}$ = 5.652, p = 0.022) and Scale of Suicidal Ideation (SSI) ($F_{5, 429}$ = 2.652, p = 0.022). Nevertheless, there was no significant time by group interaction, displaying by these four clinical measures [23]. Those showed that the effectiveness of 10Hz accelerated rTMS was not significantly different compared with 10Hz standard rTMS to dlPFC, but they were both effective in treating MDD.

A randomized controlled trial included 31 subjects who were randomly allocated to the real rTMS group (n = 15) and sham rTMS group (n = 16). For active and sham rTMS group of patients, they were randomly assigned to receive 20-session 10Hz rTMS which lasted for 30 minutes per session for four weeks. The coil was tilted 45° away from the scalp in the sham group. The antidepressant treatment in the active rTMS group (47%) was lower than that in the sham rTMS group (88%; p = 0.010). The study was stopped because none of the patients in active conditions responded to rTMS treatment. There was a main effect of time ($F_{1,30}$ = 25.4; p < 0.01), no main effect of treatment ($F_{1,30}$ = 1.5; p = 0.230) and no interaction between time and treatment ($F_{1,30}$ = 0.45; p = 0.500) [24]. These results suggested that 10Hz rTMS to left dlPFC was ineffective to treatment resistant depression comparing with sham stimulation.

A randomized controlled and double-blinded study involved 29 participants who were allocated to active (n = 8) and sham groups (n = 11). In phase 1, the researchers used visual identification of thumb twitch and initiation of treatment to obtain the consisting of motor threshold. In the blinded phase, 10Hz rTMS was delivered to dlPFC for 3000 pulses per session. There were 20 sessions in total and the treatment lasted for 5 days per week. In the sham group, the patients received rTMS with one active and one sham coil. The sham coil was the same as the active coil in shape and weight but did not transport the magnetic energy. There was a significant time by group effect in the MADRS score (p < 0.010) [25]. In other words, there was an overall decline in MADRS for the active group, while the reduction of MADRS score was not observed in the sham group. The results suggested that 10Hz rTMS to dlPFC was effective to treat MDD comparing with sham stimulation.

A randomized controlled trial included 301 patients who were randomly assigned to the active group (n = 155) and sham group (n = 146). The TMS was applied to dlPFC with a frequency of 10 pulses per second for a total of 3000 pulses. The treatment lasted 5 days per week over 6 weeks. There was no significant difference between the active and the sham group in HAMD score over each treatment point (i.e., week 2,

week 4, week 6) ($p > 0.050$) [26]. The results suggested that 10 Hz TMS applied to dlPFC did not significantly improve MDD symptoms compared to sham stimulation.

B. TMS over Both Hemisphere (i. e. Left dlpfc and Right dlPFC)

There were three studies that conducted TMS to both the left dorsolateral prefrontal cortex (dlPFC) and right dorsolateral prefrontal cortex (dlPFC). A randomized controlled study randomly assigned 56 patients to three groups. Patients in rTMS group (n = 18) received 1Hz TMS to right dlPFC, immediately followed by 10Hz TMS to left dlPFC for total 2000 stimuli in 15 subsequent days. Theta Burst stimulation (TBS) group (n=20) was treated with continuous theta burst stimulation (cTBS) to right dlPFC, immediately followed by intermittent theta burst stimulation (iTBS) to left dlPFC for a total of 2400 stimuli for 15 days. The sham group (n=18) received TBS protocol with a sham coil. There was a significant main effect of time in HAMD change between baseline and end of treatment, ($F_{1,\ 51}$ = 55.434; $p < 0.001$), but there was no significant main effect of group ($F_{2,51}$ = 0.122; p = 0.886) and no significant time by group interaction ($F_{2,51}$ = 0.862; p = 0.428). The change in HAMD for TBS was favorable than sham (d = 0.359) and rTMS group (d = 0.406) with medium effect size (defined according to Cohen's d. Data). In addition, effect size was negligible between rTMS and sham group (d = 0.088) [27]. The results indicated that TBS to both left and right dlPFC was a little bit more effective compared with 10Hz rTMS to both left and right dlPFC and sham stimulation measuring by HAMD.

A randomized controlled pilot study randomly assigned 32 patients into the sham group (n = 16) and TBS group (n = 16). Patients in the TBS group received 50Hz iTBS 20 times for 2s each 10s on the left side and 50Hz cTBS for the 40s on the right side for the working days for six weeks. The statistical results demonstrated that the response rate of the TBS group measured by MADRS was significantly higher than the sham group (p = 0.048), which was 56% and 4% respectively and the remission rate of TBS has no significant difference compared with the sham group (p = 0.079). The response and remission rate measured by HAMD of TBS and sham group was not significantly different which had p = 0.205 and p = 0.127 severally, as well as the response and remission rate measured by BDI was not significantly different between TBS and sham group, which had p = 0.245 and p = 0.058 respectively [28]. These results suggested that only the response rate measured by MADRS exhibited the effectiveness of TBS to both left and right dlPFC in treating MDD comparing with sham stimulation.

There was a study randomly assigned 37 patients into active rTMS group (n = 18) and sham group (n=19). Patients in the rTMS group were treated with 1Hz rTMS to the right hemisphere for 4 trains with 30-s interval and then 10Hz rTMS to the left hemisphere for 23 trains with 25-s interval on weekdays of 6 weeks. According to the results, four in the active group and six in the sham group were all achieved full remission (HAM-D score ≥7). The difference in the remission rate of rTMS and sham group was not significant (t(32) = -0.74; p = 0.470). Moreover, there were eight patients in the active group and 11 patients in the sham group which achieved treatment response. There was not a significant difference of treatment response in rTMS and sham group (t(32) = -1.02; p = 0.320). However, there were four patients (three in the active rTMS group and one in the sham group) that had worse depression after the 6-week rTMS treatment [29]. The results demonstrated that 1Hz rTMS to right dlPFC and 10Hz rTMS to left dlPFC was not effective in treating MDD comparing with sham stimulation.

A randomized controlled study involved 15 patients in the sham group and 15 patients in the active group. The frequency of rTMS was set at 10Hz and every treatment session lasted for 30 minutes for 15 sessions during 15 continuous weekdays. The dose of medication used for each group and the depressive symptoms of each group at baseline was not significantly different. From the ANOVA results, there was a significant main effect of time in HAM-D scores before and after rTMS treatment ($F_{1,28}$ = 45.912, $p < 0.001$, ηp^2 = 0.621). There was a significant time and group interaction ($F_{1,28}$ = 4.665, p = 0.040, ηp^2 = 0.143) as well. The improvements in clinical depressive symptoms in the active group were greater compared with the sham group (Changes of HAM-D in active rTMS: -7.13 ± 4.51; in sham rTMS: -3.68 ± 4.22) [30]. The results suggested that 10 Hz rTMS treatment to 5 cm anterior to the optimal surface site for activation of the right APB muscle in dlPFC was effective in treating MDD comparing with sham stimulation.

C. TMS over Midline Cortical Surface (i.e., Frontal Polar Region, The Superior Frontal Gyrus and Parietal Region)

A randomized, sham-controlled and double-blind study randomly assigned 52 subjects into 3 groups, including a group with active synchronized Transcranial Magnetic Stimulation (sTMS) with a fixed frequency at the alpha frequency (8 Hz and 13 Hz) ± 0.1 Hz, a group with active sTMS with a random stimulus frequency that varied between 8 Hz and 13 Hz and a group with sham sTMS. The first two groups were regarded as a single group that received active sTMS. The treatments in the sham group were similar to the active group except for the magnetic field. There were 46 patients in the active (n = 30) and sham group (n = 16) who completed the whole treatment. Patients in active group received sTMS treatment for 20 mins each session during weekdays in 5 weeks. The improvement of the active group was significantly better than the sham group measuring by HAMD-17. Additionally, the change in HAMD-17 score had a significantly time by treatment interaction between active and sham groups (Greenhouse-Geisser adjustment F1.9,85.1 = 4.100, p = 0.020) [31]. According to these results, sTMS over the midline cortical surface was effective in treating MDD comparing with sham stimulation.

D. TMS to the Visual Cortex

A double-blinded and randomized controlled study included 74 patients who were randomly assigned to an individual (individualized MRI data, n = 24), standard (structural MRI on left primary visual cortex, n = 27), sham (structural MRI on left V1 region, n = 23) and healthy control group (n = 30). Patients received rTMS with 10Hz for 20 mins per session over 5 weeks and rTMS for the individual and standard group were located at different places on the visual cortex. The treatment in the sham group was delivered by rotating the coil through 90°. After rTMS treatment (day

5), there was a significant difference in HAMD-24 in each rTMS- containing group (all $p < 0.001$, individualized group: $t = 14.498$; standard group: $t = 14.408$; sham group: t = 6.865). The response rates of the patients in the individual group were better than in the standard and sham group, but not significantly better ($\chi^2 = 5.368$, $p = 0.068$). Moreover, there was a significant time by treatment interaction in these three groups ($F = 5.53$, $p = 0.005$). According to the further investigation, the change rate of HAMD-24 in the individual group was significantly improved at day 5 ($p < 0.001$), week 1 ($p = 0.003$) and week 2 ($p = 0.009$), comparing with the sham group [32]. These suggested that 10Hz rTMS to the region which was navigated by individualized MRI data in the primary visual cortex was effective until week 2.

E. TMS over the Left Primary Motor Cortex

A randomized controlled study included 22 patients who were assigned to the MDD group ($n = 11$) and healthy controls ($n = 11$). All the patients received two sessions of treatment, including one session of cTBS and one session of iTBS. The cTBS stimulation was composed of 3 pulses every 200ms for the 40s with the frequency of 50Hz for a total of 600 pulses, while the iTBS stimulation paradigm consisted of a 2-second train repeating every 10 seconds for 190 seconds (600 pulses) in total. There was a significant group by time interaction when patients received iTBS ($F_{4,21} = 2.504$, $p = 0.049$). The post-hoc comparison demonstrated that there was a significant difference between patients and healthy controls after 20-min iTBS ($p = 0.038$).There was no significant difference between depressed participants and healthy controls at other time point (5 min: $p = 0.193$; 10 min: $p = 0.130$; 30 min: $p = 0.406$). However, there was no significant group by time interaction when patients received the cTBS treatment ($F_{4,22} = 0.986$, $p = 0.420$). Also, there was no significant difference between these two groups in responders ($p = 1.000$) [33]. The results suggested that 15Hz iTBS to the point 5.0 cm anterior to the site of the motor cortex that maximally stimulated the right first dorsal interosseous muscle was effective in treating MDD.

F. TMS was Applied over the Hand Area of Primary Motor Cortex

There was a randomized controlled trial that included 63 patients who were randomly assigned to an active TMS group ($n = 32$) and a sham group ($n = 31$). Participants in the active group received 10Hz TMS for 160 pulses per session over 2 weeks for 24,000 pulses in total. The sham group received the same manner as the active group whereas the coil was positioned 90° away from the scalp. According to the HDRS scores, the response rates of the TMS and sham groups were significantly different ($p = 0.008$), which were 30.6% and 6.1% respectively. The remission rates of the active and sham groups had a significant difference ($p = 0.033$), which were 20% and 3% separately [34]. The results suggested that 10Hz TMS to the hand area of the primary motor cortex was effective in reducing the MDD symptoms comparing with sham stimulation.

G. TMS over Left dlPFC and Dorsomedial Prefrontal Cortex (dmPFC)

A randomized controlled and double-blinded study was completed in 92 intent-to-treat patients who were randomly allocated to the active group (n = 47) and sham group ($n = 45$). Some of the patients withdraw due to disagreement, removing by study physician and other reasons. Research was done to all the patients and patients who do not withdraw during the treatment ($n = 84$) respectively. The rTMS was delivered by 10Hz with the 30s for a train and 3000 pulses per session. The treatment had 20 sessions in total for 4-6 weeks and a one-month follow-up visit. The results showed that in the 92 patients, the change in HAMD-24 of the active group and sham group was not significantly different (p = 0.145). In the 84 patients, the change in HAMD-24 of the active group was significantly greater than the change in HAMD-24 of the sham group (-15.1 ± 9.6 vs. -10.4 ± 8.7, $p = 0.030$) and the reduction in depression scores of the active group was significantly greater than that of sham group ($F = 6.748$, $p = 0.010$) [35]. The results suggested that 10Hz rTMS to left dlPFC and dmPFC was effective to treat MDD comparing with sham stimulation.

IV. Conclusion

TMS is a non-pharmacologic treatment alternative to treat different kinds of psychological disorders like depression. Although this kind of treatment can have some side effects like dizziness, headaches, vision problems, it brings lots of benefits for patients who are treatment resistant to traditional therapies and medications. In this systematic review, 18 studies were included: 12 rTMS, 1 dTMS, 1 rTMS and TBS, 1 sTMS, 2 iTBS and cTBS, 1 iTBS. A majority of studies showed high-frequency rTMS (10 Hz) was effective to left dlPFC, primary visual cortex, hand area of the primary motor cortex, left dlPFC and dmPFC. However, there were three studies that showed high-frequency rTMS was not effective: one is to apply 1Hz rTMS to right and 10Hz rTMS to the left hemisphere, one is to perform 10 Hz rTMS to left dlPFC to treat treatment resistant depression and another is to perform 10Hz TMS to left dlPFC. Moreover, 18Hz dTMS to left dlPFC and sTMS (8 Hz-13 Hz) over midline cortical surface both were effective. Additionally, 15Hz iTBS to the left primary motor cortex was effective, while TBS to both hemispheres was not always effective. Furthermore, there was one study that suggested that rTMS with a H1-coil was more effective than a figure-to-8 coil. The limitations of this systematic review are that some single-blinded studies are reviewed and only focus on the treatment of adult patients. Hence, more double-blinded trials and trials that focus on other social groups should be evaluated. Generally speaking, the evidence for TMS treatment is reliable and it has a bright prospect to be used widely in clinical medicine.

References

[1] American psychiatric association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). [Online]. Available: https://doi.org/10.1176/appi.books.9780890425596J. U. Duncombe

[2] "Depression and other common mental disorders: Global health estimates," Geneva: World Health Organization; 2017.

[3] P. S. Wang, S. A. Gaxiola, J. Alonso, M. C. Angermeyer, G. Borges, E. J. Bromet, R. Bruffaerts, G. D. Girolamo, R. D. Graaf *et al*. (2007). Use of mental health services for anxiety, mood, and substance disorders in 17 countries in the WHO world mental health surveys. Lancet (London, England). [Online]. Available: https://doi.org/10.1016/S0140-6736(07)61414-7

[4] K. Stroud. (2010). Stressful life events and major depression. [Online]. Available:

https://www.family-institute.org/behavioral-health-resources/stressful-life-events-and-major-depression
[5] L. Bowes, C. Joinson, D. Wolke, and G. Lewis. (2015). Peer victimisation during adolescence and its impact on depression in early adulthood: prospective cohort study in the United Kingdom. [Online]. Available: https://doi.org/10.1136/bmj.h2469
[6] P. McGuffin, R. Katz, and P. Bebbington, "The camberwell collaborative depression study, depression and adversity in the relatives of depressed probands," *The British Journal of Psychiatry: The Journal of Mental Science*, vol. 152, pp. 775–782, 1988.
[7] D. A. Collier, G. Stöber, T. Li, A. Heils, M. Catalano, D. Di Bella *et al.*, "A novel functional polymorphism within the promoter of the serotonin transporter gene: Possible role in susceptibility to affective disorders," *Molecular Psychiatry*, vol. 1, no. 6, pp. 453–460, 1996.
[8] N. Risch, R. Herrell, T. Lehner, K. Y. Liang, L. Eaves, J. Hoh, A. Griem, M. Kovacs, J. Ott, and K. R. Merikangas, "Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: A meta-analysis," *JAMA*, vol. 301, no. 23, pp. 2462–2471, 2009.
[9] I. Kirsch, B. J. Deacon, T. B. Huedo-Medina, A. Scoboria, T. J. Moore, and B. T. Johnson, "Initial severity and antidepressant benefits: A meta-analysis of data submitted to the food and drug administration," *PLoS Medicine*, vol. 5, no. 2, 2008.
[10] M. H. Trivedi, A. J. Rush, S. R. Wisniewski, A. A. Nierenberg, D. Warden, L. Ritz, G. Norquist, R. H. Howland, B. Lebowitz, P. J. McGrath, K. S. Wilson, M. M. Biggs, G. K. Balasubramani, and M. Fava, "Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice," *The American Journal of Psychiatry*, vol. 163, no. 1, pp. 28–40.
[11] J. Iddon and L. Grant, "Behavioural and cognitive treatment interventions in depression: An analysis of the evidence base," *Open Journal of Depression*, vol. 2, pp. 11-15, 2013.
[12] R. King, "Cognitive therapy of depression," *The Australian and New Zealand Journal of Psychiatry*, vol. 36, no. 2, pp. 272–275, 2002.
[13] M. Hallett. (2007). Transcranial Magnetic Stimulation: A Primer. Neuron. [Online]. Available: https://doi.org/10.1016/j.neuron.2007.06.026
[14] Stilling, J. M., Monchi, O., Amoozegar, F., & Debert, C. T. (2019). Transcranial Magnetic and Direct Current Stimulation (TMS/tDCS) for the Treatment of Headache: A Systematic Review. [Online]. Available: https://doi.org/10.1111/head.13479
[15] J. L. R. Martin, J. M. Barbanoj, T. E. Schlaepfer, S. S. C. Clos, V. Pérez, J. Kulisevsky, and A. Gironelli, "Transcranial magnetic stimulation for treating depression," *Cochrane Database of Systematic Reviews*, 2001.
[16] A. Somani and S. K. Kar, "Efficacy of repetitive transcranial magnetic stimulation in treatment-resistant depression: The evidence thus far," *General Psychiatry*, vol. 32, no. 4, 2019.
[17] R. Magnezi, E. Aminov, D. Shmuel, M. Dreifuss, and P. Dannon, "Comparison between neurostimulation techniques repetitive transcranial magnetic stimulation vs electroconvulsive therapy for the treatment of resistant depression: Patient preference and cost-effectiveness," *Preference and Adherence*, vol. 10, pp. 1481–1487, 2016.
[18] M. J. Page, J. E. McKenzie, P. M. Bossuyt *et al*., "The PRISMA 2020 statement: An updated guideline for reporting systematic reviews," *Syst Rev*, vol. 10, no. 89, 2021.
[19] F. J. Chen, C. Z. Gu, N. Zhai, H. F. Duan, A. L. Zhai, and X. Zhang, Repetitive Transcranial Magnetic Stimulation Improves Amygdale Functional Connectivity in Major Depressive Disorder, Frontiers in psychiatry, 2020.
[20] I. Filipčić, I. Š. Filipčić, Z. Milovac, S. Sučić, T. Gajšak, E. Ivezić, S. Bašić, Z. Bajić, and M. Heilig, "Efficacy of repetitive transcranial magnetic stimulation using a figure-8-coil or an H1-Coil in treatment of major depressive disorder, A randomized clinical trial," *Journal of Psychiatric Research*, vol. 114, pp. 113–119, 2019.
[21] S. Lee, K. I. Jang, and J. H. Chae, "Association of the loudness dependence of auditory evoked potentials with clinical changes to repetitive transcranial magnetic stimulation in patients with depression," *Journal of Affective Disorders*, vol. 238, pp. 451–457, 2018.
[22] H. N. Wang, X. X. Wang, and R. G. Zhang *et al*., "Clustered repetitive transcranial magnetic stimulation for the prevention of depressive relapse/recurrence: A randomized controlled trial," *Translational Psychiatry*, vol. 7, no. 12, 2017.
[23] Y. Levkovitz, M. Isserles, F. Padberg, S. H. Lisanby, A. Bystritsky *et al.*, "Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial," *World Psychiatry: Official Journal of the World Psychiatric Association*, vol. 14, no. 1, pp. 64–73, 2015.
[24] F. Pan, Z. Shen, J. Jiao, J. Chen, S. Li, J. Lu, J. Duan, N. Wei, D. Shang *et al.*, "Neuronavigation-guided rTMS for the treatment of depressive patients with suicidal ideation: A double-blind, randomized, sham-controlled trial," *Clinical Pharmacology and Therapeutics*, vol. 108, no. 4, pp. 826–832, 2020.
[25] P. B. Fitzgerald, K. E. Hoy, D. Elliot, R. N. S. McQueen, L. E. Wambeek, and Z. J. Daskalakis, "Accelerated repetitive transcranial magnetic stimulation in the treatment of depression," *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, vol. 43, no. 7, pp. 1565–1572, 2018.
[26] V. P. Eijndhoven, J. Bartholomeus, M. Möbius, D. A. Bruijn *et al.* "A randomized controlled trial of a standard 4-week protocol of repetitive transcranial magnetic stimulation in severe treatment resistant depression," *Journal of Affective Disorders*, vol. 274, pp. 444–449, 2020.
[27] S. N. Light, L. A. Bieliauskas, and S. F. Taylor, "Measuring change in anhedonia using the "Happy Faces" task pre- to post-repetitive transcranial magnetic stimulation (rTMS) treatment to left dorsolateral prefrontal cortex in major depressive disorder (MDD): Relation to empathic happiness," *Translational Psychiatry*, vol. 9, no. 1, 2019.
[28] P. B. Rosenquist, A. Krystal, K. L. Heart, M. A. Demitrack, and W. V. McCall, "Left dorsolateral prefrontal transcranial magnetic stimulation (TMS): Sleep factor changes during treatment in patients with pharmacoresistant major depressive disorder," *Psychiatry Research*, vol. 205, no. 1-2, pp. 67–73, 2013.
[29] J. Prasser, M. Schecklmann, T. B. Poeppl, E. Frank, P. M. Kreuzer, G. Hajak, R. Rupprecht, M. Landgrebe, and B. Langguth, "Bilateral prefrontal rTMS and theta burst TMS as an add-on treatment for depression: A randomized placebo-controlled trial. The world journal of biological psychiatry," *The Official Journal of the World Federation of Societies of Biological Psychiatry*, vol. 16, no. 1, pp. 57–65, 2015.
[30] C. Plewnia, P. Pasqualetti, S. Große, S. Schlipf, B. Wasserka, B. Zwissler, and A. Fallgatter, "Treatment of major depression with bilateral theta burst stimulation: A randomized controlled pilot trial," *Journal of Affective Disorders*, vol. 156, pp. 219–223, 2014.
[31] M. V. Korhonen, H. Leinola, M. Könönen, E. Niskanen, M. Purhonen, M. Pakarinen, A. Ruusunen, S. M. Lehto, E. Mervaala, K. Honkalampi, H. K. Honkanen, and H. Viinamäki, "Bifrontal active and sham rTMS in treatment-resistant unipolar major depression," *Nordic journal of Psychiatry*, vol. 72, no. 8, pp. 586–592, 2018.
[32] Y. Jin, and B. Phillips, "A pilot study of the use of EEG-based synchronized transcranial magnetic stimulation (sTMS) for treatment of major depression," *BMC Psychiatry*, vol. 14, 2014.
[33] Z. Zhang, H. Zhang, C. M. Xie, M. Zhang, Y. Shi, R. Song, X. Lu *et al*., "Task-related functional magnetic resonance imaging-based neuronavigation for the treatment of depression by individualized repetitive transcranial magnetic stimulation of the visual cortex," *Science China Life Sciences*, vol. 64, no. 1, pp. 96–106, 2021,
[34] C. Wajdik, K. H. Claypoole, W. Fawaz, P. E. Holtzheimer *et al*., "No change in neuropsychological functioning after receiving repetitive transcranial magnetic stimulation treatment for major depression," *The Journal of ECT*, vol. 30, no. 4, pp. 320–324, 2014.
[35] L. L. Carpenter, S. T. Aaronson, G. N. Clarke *et al.*, (2017). "rTMS with a two-coil array: Safety and efficacy for treatment resistant major depressive disorder," *Brain Stimulation*, vol. 10, no. 5, pp. 926–933, 2017.

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