Response trajectory of acute effects to long-term after-effects to left dorsolateral prefrontal rTMS in major depressive disorder: a meta-analysis of randomized controlled trials

Tien-Wei Hsu[1,2,#], Ta-Chuan Yeh[3,#], Yu-Chen Kao[4,5], Trevor Thompson[6], Andre R. Brunoni[7,8], Andre F. Carvalho[9], Yu-Kang Tu[10,11], Ping-Tao Tseng[12,13,14,15], Chia-Ling Yu[16], Shu-Li Cheng[17,*],Chih-Sung Liang[4,5,*]

1. Department of Psychiatry, E-DA Dachang Hospital, Kaohsiung, Taiwan
2. Department of Psychiatry, E-DA Hospital, Kaohsiung, Taiwan
3. Department of Psychiatry, Tri-Service General Hospital, National Defense Medical Centre, Taipei, Taiwan
4. Department of Psychiatry, National Defense Medical Centre, Taipei, Taiwan
5. Department of Psychiatry, Beitou Branch, Tri-Service General Hospital, Taipei, Taiwan
6. Centre for Chronic Illness and Ageing, University of Greenwich, London, UK
7. Service of Interdisciplinary Neuromodulation, Laboratory of Neurosciences (LIM-27), Instituto de Psiquiatria, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo 05403-010, Brazil
8. Service of Electroconvulsive Therapy, Instituto de Psiquiatria, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo 05403-010, Brazil
9. IMPACT (Innovation in Mental and Physical Health and Clinical Treatment) Strategic Research Centre, School of Medicine, Barwon Health, Deakin University, Geelong, VIC, Australia
10. Institute of Epidemiology & Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan
11. Department of Dentistry, National Taiwan University Hospital, Taipei, Taiwan
12. Institute of Biomedical Sciences, National Sun Yat-sen University, Kaohsiung, Taiwan
13. Department of Psychology, College of Medical and Health Science, Asia University, Taichung, Taiwan
14. Prospect Clinic for Otorhinolaryngology & Neurology, Kaohsiung, Taiwan
15. Institute of Precision Medicine, National Sun Yat-sen University, Kaohsiung City, Taiwan
16. Department of Pharmacy, Chang Gung Memorial Hospital Linkou, Taipei, Taiwan
17. Department of Nursing, Mackay Medical College, Taipei, Taiwan

[#] contributed equally to this article as first author

* contributed equally to this article as corresponding author

* Please corresponding to:
Chih-Sung Liang, MD
Department of Psychiatry, Beitou Branch, Tri-Service General Hospital; School of Medicine, National Defense Medical Center, Taipei, Taiwan
No. 60, Xinmin Road, Beitou District, Taipei City 112, Taiwan
Tel: 886-2-28959808
Email: lcsyfw@gmail.com
ORCID: 0000-0003-1138-5586

ABSTRACT

The depression response trajectory after a course of repetitive transcranial magnetic stimulation(rTMS) remains understudied. We searched for blinded randomized controlled trials(RCTs) that examined conventional rTMS over left dorsolateral prefrontal cortex(DLPFC) for major depressive episodes(MDE). The effect size was calcu- lated as the difference in depression improvement, between active and sham rTMS. We conducted a random- effects dose-response meta-analysis to model the response trajectory from the beginning of rTMS to the post- treatment follow-up phase. The area under curve (AUC) of the first 8-week response trajectory was calculated to compare antidepressant efficacy between different rTMS protocols. We included 40 RCTs(n = 2012). The best- fitting trajectory model exhibited a logarithmic curve($X2=17.7$, $P < 0.001$), showing a gradual ascent with tapering off around the 3–4th week mark and maintaining until week 16. The maximum effect size was 6.1(95 % CI: 1.25–10.96) at week 16. The subgroup analyses showed distinct trajectories across different rTMS protocols. Besides, the comparisons of AUC showed that conventional rTMS protocols with more pulse/session group or more total pulses were associated with greater efficacy than those with fewer pulse/session or fewer total pulses, respectively. A course of conventional left DLPFC rTMS could lead to both acute antidepressant effects and sustained after-effects, which were modeled by different rTMS protocols in MDE.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation technique that has been widely used for the treatment of major depressive disorder (MDD) (Mutz et al., 2019). In 2008, the United States Food and Drug Association (FDA) approved rTMS over the left dorsolateral prefrontal cortex (DLPFC) for treatment-resistant depression (TRD) (O'Reardon et al., 2007). However, the depression response trajectory from the beginning of rTMS treatment to post-treatment follow-up phase remains understudied.

A previous meta-analytic study assessed response rate following acute rTMS and found approximately a 70 % response rate within three months, declining to 50 % within six months (Senova et al., 2019). However, this study's findings were limited, because (i) it pooled the outcomes of studies with and without maintenance treatment, (ii) only followed the responders, and (iii) did not assess the continuous changes in depressive symptoms but only the dichotomous response (Senova et al., 2019). Another previous meta-analysis examined the continuous changes in depressive symptoms (Brian Chen et al., 2023). However, this study (i) also pooled outcomes of studies with and without maintenance treatment, (ii) included non-RCT studies, (ii) used follow-up data only from rTMS group without data from the sham group, and (iv) only examined depression severity during the follow-up phase. Therefore, several questions remain unclear. For instance, is the depression response curve during acute rTMS phase and post-treatment phase a linear curve? How do the rTMS protocols affect the response trajectory?

Pharmacological antidepressant treatments have demonstrated a non-linear pattern of response, characterized by substantial symptom improvements in the initial weeks, followed by more gradual enhance- ments approaching a plateau (Posternak and Zimmerman, 2005; Taylor et al., 2006). There are relatively fewer studies utilizing meta-analysis to integrate and analyze the treatment response of rTMS. To address this knowledge gap, we conducted a dose-response meta-analysis to inves- tigate the trajectory of continuous depressive symptoms from the initi- ation of acute conventional rTMS treatments to the follow-up period. We also assessed the influence of different rTMS parameters on the response trajectory. Out focus was on blinded RCTs that utilized conventional rTMS over the left DLPFC and assessed depression changes in both active and sham rTMS groups without maintenance treatment. In clinical practice, understanding how individuals' responses to treatment change over time can help therapists better assess treatment progress and adjust treatment strategies to meet patients' needs and to ensure optimal care. This is particularly important for treating conditions such as depression, anxiety disorders, and other mental health illness.

2. Methods

2.1. Study design

We conducted a systematic review and dose-response meta-analysis to include all RCTs comparing conventional rTMS over the left DLPFC with sham rTMS for patients with MDD. The protocol of the current study was a priori registered with Open Science Framework (OSF) (10.17605/OSF.IO/TEX9U). This study followed the Preferred Report- ing Items for Systematic Reviews and Meta-Analyses guidelines (Ap- pendix 1) (Page et al., 2021). Ethical approval was waived for this study.

2.2. Search strategy

The MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, PsycINFO, and ClinicalTrial.gov databases were systematically searched without language restrictions from database inception to August 13, 2023. Additionally, we searched grey literature databases and manually searched the reference lists of relevant reviews. Two independent authors screened the titles and abstracts of all retrieved references for potentially eligible articles, and any disagreement was resolved by a third authors. Appendix 2 demonstrates the complete search strategies, and appendix 3 shows the reasons for exclusion.

2.3. Eligibility criteria

The PICOS (population, intervention, comparison, outcome, and study) applied in this study was as follows: (i) P: patients with MDD; (ii) I: conventional rTMS over the left DLPFC; (iii) C: sham control; (iv) O: changes in depressive symptoms; and (v) S: blinded RCT. We excluded: (i) open-label trials or non-RCT studies; (ii) studies focusing on sec- ondary depression, such as post-stroke depression or Parkinson-related depression; (iii) maintenance treatment or relapse prevention studies; (iv) combination treatment with other brain stimulation sites or pro- tocols; (v) head-to-head studies without any sham controls; and (vi) studies that did not report depressive symptoms on a continuous scale. Studies with only two measurements of depression changes were excluded (i.e., baseline and end of study), because such studies could not provide reliable data on response trajectory.

2.4. Outcome definition and data extraction

Intention-to-treat datasets were used when available. The outcome of interest was the difference in depression improvement between active rTMS and sham rTMS groups. The included studies used the following measurement tools: the Hamilton Rating Scale for Depression (HDRS) (17, 21, 24, 25, 28-items) (Hamilton, 1967), Montgomery-Åsberg Depression Rating Scale(Montgomery and Asberg, 1979), Beck Depres- sion Inventory (second edition) (Beck et al., 1996), or quick inventory of depressive symptomatology (16-items) (Rush et al., 2003). We extracted scores (means and standard deviation) of depressive symptoms at baseline, end of treatment, and other time point

measurements. To enhance interpretability, all the extracted scores were converted to the corresponding scores of the 17-item HDRS (HDRS-17) using a validated method (Thorlund et al., 2011). We also extracted the first author's name, publication year, sample size, sex, age, rTMS protocols (fre- quency, pulses per session, total sessions, intensity, total pulses, methods of sham control, and stimulation duration (i.e., active rTMS duration)), diagnosis, treatment strategy (augmentation with medication, mono- therapy, or mixed), and diagnoses (major depression or bipolar depression). For studies that reported effect estimates graphically, we used the WebPlotDigitizer online tool (www://plotdigitizer.source- forge.net/) to estimate the effect estimates from the graphs. Data extraction was completed independently by two authors and cross-checked for errors.

2.5. Quality assessment

The Cochrane Risk of Bias Assessment Tool(Higgins et al., 2011) was utilized to evaluate the quality of the RCTs. The included studies were classified as having a high, low, or unclear risk of bias (ROB) according to the following domains: randomization, allocation concealment, detection bias, performance bias, attrition bias, and reporting bias. Two authors independently conducted this assessment and discrepancies were resolved by consensus.

2.6. Statistical analyses

We utilized the mean difference of depression improvement (sub- tracting the scores measured afterward from the baseline scores) be- tween the rTMS group and the sham control group as the metric for effect size. We performed a single-stage, random-effects, dose-response meta-analysis to summarize, across studies, the relationship between time point and the rTMS effect sizes (Crippa and Orsini, 2016). Linear, quadratic, and spline models were examined. The spline models were analyzed using restricted cubic splines (RCSs) with three knots according to Harrell's recommended centiles (10 %, 50 %, and 90 %) of distribution (Harrell and Harrell, 2015). We then assessed if the trajec- tory response could be clustered into different trends using longitudinal K-means methodology(Genolini and Falissard, 2010). If different lon- gitudinal trajectories may exist, we performed subgroup analysis to identify potential moderators for the response trajectory. The investi- gated moderators included intensity, frequency, pulse/session, stimu- lation duration, total sessions, total pulses, a diagnosis of TRD, mixed diagnosis (pure MDD vs. mixed with bipolar depression and MDD), and monotherapy (added-on vs. monotherapy vs. mixed). The time frame utilized in the current study ranged from the baseline assessment (week 0) to the final follow-up period after treatment. For instance, in a study employing a 2-week stimulation protocol and subsequently tracking participants for 4 weeks, the study's duration encompassed weeks 0 through week 6. We calculated the area under the curve (AUC) of the first 8 weeks of the response trajectory (from the beginning of acute rTMS treatment until week 8). This approach was chosen because a typical course of rTMS usually spans a 2-week stimulation period (i.e., from week 0 to

week 2), and published data typically measured post-treatment depression severity 2 to 6 weeks after treatment completion (i.e., from week 2 to week 8). The AUC may indicate the first two months of antidepressant outcome of an acute rTMS treatment. All analyses were performed using R (version 4.1.1) in R Studio (version 2023.06.1 + 524) and GraphPad Prism statistical software (GraphPad Prism, version 8) software. All comparisons were two-tailed, and a p-value cut-off point of 0.05 denoted statistical significance.

3. Results

3.1. Characteristics and quality of included study

Our searches resulted in 2399 potentially relevant citations (eFig- ure1). The complete search strategies and reasons for the exclusion of certain studies can be found in Appendices 2 and 3. After removing duplicates, 40 eligible RCTs (46 intervention arms, n = 2012) were included. The details of the characteristics of the included studies are provided in eTable 1. Overall, 1060 participants were randomized to the active rTMS group (mean age: 45.9 (8.0) years; females: 61.6 %) and 952 to the sham rTMS group (mean age: 46.5 (8.9) years, females: 58.9%). Fig. 1 demonstrates the distribution of rTMS protocols of the included RCTs. Most studies used 10 Hz stimulation frequency (48 %), and the second most commonly used were 20 Hz (35 %; Fig. 1A). Additionally, a total of 10 sessions and 2-week stimulation duration were the mostly used protocols (both 41 %; Fig. 1B and 1C). For intensity (motor threshold (MT)), 28 % studies used 110 % MT, 22 % used 100 % MT, and 17 % used 120 % MT (Fig. 1D). After the end of the rTMS treatment, the follow-up duration ranged between 1 week and 12 weeks (Fig. 1E). Finally, most studies used 800 pulse/session or 1600 pulse/ session (12 trials for each; Fig. 1F), and 16,000 total stimulation pulses was the mostly used rTMS protocol (9 trials; Fig. 1G).

3.2. Quality of the included studies

Four studies (4/40=10 %) were rated as having a high overall ROB (eFigure 2 and eFigure 3). The percentage of studies with high, unclear, and low ROB for the individual items were as follows: 0 %, 42.5 %, and 57.5 % for randomization; 0 %, 72.5 %, and 27.5 % for allocation concealment; 2.5 %, 25 %, and 72.5 % for blinding of participants and personnel; 2.5 %, 12.5 %, and 85 % for blinding of outcome assessment; 5 %, 2.5 %, and 92.5 % for incomplete outcome data; and 0 %, 2.5 %, and 97.5 % for selective reporting.

3.3. Trajectory of depressive symptoms after a course of rTMS treatment

Compared to linear (eTable 2, $\chi 2=2599$, $P < 0.001$) and quadratic (eTable 2, $\chi 2=47.5$, $P < 0.001$), the best fitting model for the response trajectory was a logarithmic curve (Fig. 2A, $X2=17.7$, $P < 0.001$), showing a gradual ascent with tapering off around week 3 to week 4, and maintaining a slow, steady increase until week 16. The maximum effect size was 6.1 (95 %CI: 1.25–10.96), occurring at week 16 (95 % confi- dence interval: 3.68–16). When considering the active rTMS arms and sham rTMS arms

separately (Fig. 2B), the response trajectory curves were similar between these two groups.

3.4. Subgroup analysis of depression response trajectory

The plot (eFigure 4) of longitudinal k-means showed that there were potential different trends of trajectories. The subgroup analyses of potential moderators found that the 4-week stimulation group demon- strated a logarithmic-like curve, with maintaining a slow, steady decrease after reaching a plateau (Fig. 2C). The maximum efficacy appeared to occur after the end of rTMS protocols of 1-week, 2-week, and 3-week stimulation groups. For the different protocol of total ses- sions (Fig. 2D). the trajectory of the total-30-session group was a loga- rithmic curve (Fig. 2D). Regarding the different protocol of pulse/ session (eFigure 5A), the high pulse/session group (≥3000) and the low pulse/session group(<1500) both exhibited logarithmic-like curve, with maintaining a slow, steady decrease after reaching a plateau. For the different protocol of total pulses (eFigure 5B), the high- (≥45,000) and low- (15,000–44,999) total-pulses groups showed logarithmic curves, while the very-low-total-pulses group (<15,000) was a logarithmic-like curve, with maintaining a slow, steady decrease after reaching a plateau. In the subgroup analysis of stimulation intensity (eFigure 5C), the group with >100 % MT showed a logarithmic-like curve, while the other groups showed ascending curves with limited time point data. rising. The subgroup analyses for stimulation frequency (eFigure 5D), a diag- nosis of TRD (eFigure 5E), diagnoses of MDD (major depression vs. mixed with bipolar depression; eTable 2), and whether combination with medication (add-on therapy vs. monotherapy vs. mixed; eTable 2) were not statistically significant (both $P > 0.05$). Further details of the subgroup analyses could be found in the eTable 2.

3.5. Area under trajectory curve (The first two months of antidepressant outcome)

The AUC of the response trajectory may indicate the total benefits (antidepressant efficacy over time) of a typical rTMS treatment within the first two months. The AUC was 53.1 in the ≥3000 pulse/session group and 18.6 in the <1500 pulse/session group (Fig. 3A), and the AUC was 60.3 in the ≥45,000 total pulses group and 18.6 in the <15,000 total pulses group (Fig. 3B).

4. Discussion

This is the first study to characterize the response trajectory from the beginning of acute conventional rTMS to several weeks after dis- continuing rTMS among patients with MDE. The main findings are as follows. First, the response trajectory was a logarithmic curve, sug- gesting that the depressive symptoms scores improved in the first weeks, then gradually leveled off, and continued to be sustained afterward. Second, when separately examining active rTMS arms and sham rTMS arms, both response trajectories exhibited similar logarithmic curves. This implies that the sustained after-effects of rTMS could not be explained only by a placebo effect. Third, the subgroup analyses show distinct response trajectories across different rTMS protocols. However, the majority of protocols still exhibit logarithmic curves.. Fourth, the first two months of antidepressant outcome may be positively associated with rTMS protocols of higher pulse/session and total pulses.

Our study found that the maximum efficacy appeared to occur during the 3rd to 4th week, and the positive ascending slope during acute rTMS phase may suggest a dose-response relationship between depression reduction and stimulation duration. The peak effectiveness was observed after end of rTMS treatment for the 1-week, 2-week, and 3- week stimulation protocols. This finding reflected the trait of delayed effects of rTMS (Pell et al., 2011). Typically, rTMS induces delayed effects that last from minutes to hours when applying single session on the motor cortex and assessing the muscle reflection (Fujiwara and Roth- well, 2004). When applying repeated sessions and measuring behavioral outcomes (e.g., depression), the delayed effects might last for days to weeks (Avery et al., 2006; Chen et al., 2013; Manes et al., 2001). A possible explanation is that rTMS would not only directly influence the ion channel on neurons but also affect the neurotransmitters and their receptors. For instance, it could lead to increased binding indices of 5-HT2A receptors in the DLPFC (Baeken et al., 2011), reduced binding of dopamine receptors in the anterior cingulate cortex (Cho and Strafella, 2009), and activation of BDNF–Trkβ signaling pathways (Wang et al., 2011). These effects may take some time to influence the clinical out- comes (Cirillo et al., 2017). A neuroimage study also reported the delayed effects of rTMS. Hayashi et al. used 5 Hz rTMS on a monkey model and performed repeated fluorodeoxyglucose positron emission tomography to follow the glucose metabolism in the brain (Hayashi et al., 2004). They found that glucose metabolism increased in limbic area after up to 8 days following rTMS course. Another possible expla- nation is the cumulative effect. A previous study showed that rTMS led to cumulative plastic changes of motor cortex excitability when repeated within 24 h (Baumer et al., 2003). When treating MDD, rTMS usually involves consecutive days of stimulation. However, unlike motor cortex excitability, depression may require more time to achieve neuro- plasticity(Chen et al., 2013; Dalhuisen et al., 2021).

We also found that after the end of the rTMS, the response trajectory is a flat pattern, representing a sustainable after-effects during the follow-up phase. The sustained improvement of depressive symptoms is consistent with a previous dose-response meta-analysis (Brian Chen et al., 2023). This meta-analysis included several prospective and retrospective cohort studies with or without maintenance rTMS treat- ment (Brian Chen et al., 2023), implying that the long-term depres- sion-reducing effects were sustained for several weeks. Moreover, in our study, the logarithmic curve of response trajectory was not only observed in the active rTMS arms but also in the sham rTMS arms. After the plateau of the logarithmic curves (about 3rd to 4th week), the changes in HDRS-17 score from baseline in the active rTMS arms continued to show a gradual and sustained increase from about 11 points to about 14 points. Meanwhile, those in the sham arms exhibited a gradual decrease from 6 points to 5 points. This finding suggested that the sustained after-effects of rTMS could not be explained only by a placebo effect. On the other hand, a 3-month follow-up functional magnetic resonance imaging (fMRI) study investigated the functional connectivity between the DLPFC and the subgenual cingulate cortex (sgACC) after rTMS treatment, and this study suggested that rTMS- associated longitudinal changes in these brain circuits was associated with treatment

response in depression (Ge et al., 2020). A review article indicates that the increased functional connectivity between the DLPFC and sgACC was associated with rTMS treatment for depression (Taib et al., 2018). However, the DLPFC-sgACC functional connectivity decreased among TRD patients in the 3-month follow-up, indicating the influence of rTMS decayed within three months (Ge et al., 2020). The mechanisms underlying the sustained antidepressant effect of rTMS remains to be determined.

When considering the AUC under the trajectory curve, the high-pulse group (i.e., pulses/session and total pulses) showed greater benefit than low-pulse group during both the acute treatment and the long-term follow-up phases. A recent meta-analysis including 52 RCTs of rTMS over left DLPFC reported that daily pulses was positively correlated with acute antidepressant efficacy by using meta-regression and subgroup analyses (Yu et al., 2023). Our findings further confirmed the high-pulse rTMS protocol may have better after-effects during the follow-up phase compared to the low-pulse rTMS protocol. Another meta-analysis including 30 RCTs of rTMS over left DLPFC also reported a dose-response relationship between total sessions (5, 10, 15, 20) and acute depression reducing effect by subgroup analyses (Teng et al., 2017). The high-pulses-dependent pattern of rTMS treatment might be due to changes in synaptic connections analogous to long-term poten- tiation, presenting the cumulative effect (Pell et al., 2011; Platz and Rothwell, 2010). However, a large clinical trial compared high-frequency rTMS between the standard daily dose group (3000 pulses/ session) and high daily dose group (5625 pulses/ session), and this study did not find significant difference between these two groups in acute antidepressant effect (Fitzgerald et al., 2020). This means that the pulse-associated dose effect may be nonlinear or approach a plateau after a certain dose.

Our study has several limitations. First, there was limited data on the progression of depression severity beyond the first 8 weeks. Second, our analysis was limited by the small sample sizes of certain included studies. The confidence intervals of trajectory after the 8th week were wide. Third, some subgroups contained few trials, leading to unex- plainable and unpredictable trajectories in these subgroups. Fourth, we did not assess the influence of demographics such as age, percentage of sex, or baseline depression severity, because those data were at the trial level, not the individual level. Details on other possible moderators, including combination medication, psychotherapy, or navigation methods were not assessed either. Lastly, to eliminate heterogeneity, we only included trials with conventional rTMS over left DLPFC. Our study findings cannot be generalized to other rTMS protocols, such as right rTMS, deep TMS, or theta burst stimulation.

5. Conclusion

We characterized the trajectory of depression response from the beginning of acute rTMS treatment to long-term follow-up after end of conventional rTMS treatment in patients with MDE. After a typical rTMS treatment over the left DLPFC, the acute antidepressant effects and the after-effects may be sustained, forming a logarithmic curve. More than 3000 pulses/ session and more

than 45,000 total pulses were significant predictors associated with greater antidepressant effects in the first 8 weeks after rTMS treatments. However, there were distinct trajectories across different rTMS protocols with different combination of parame- ters. Mapping the progression of depression severity during and after an acute conventional rTMS treatment can provide a better understanding of prognosis prediction and suggestions for parameter settings for future research and clinical practice.

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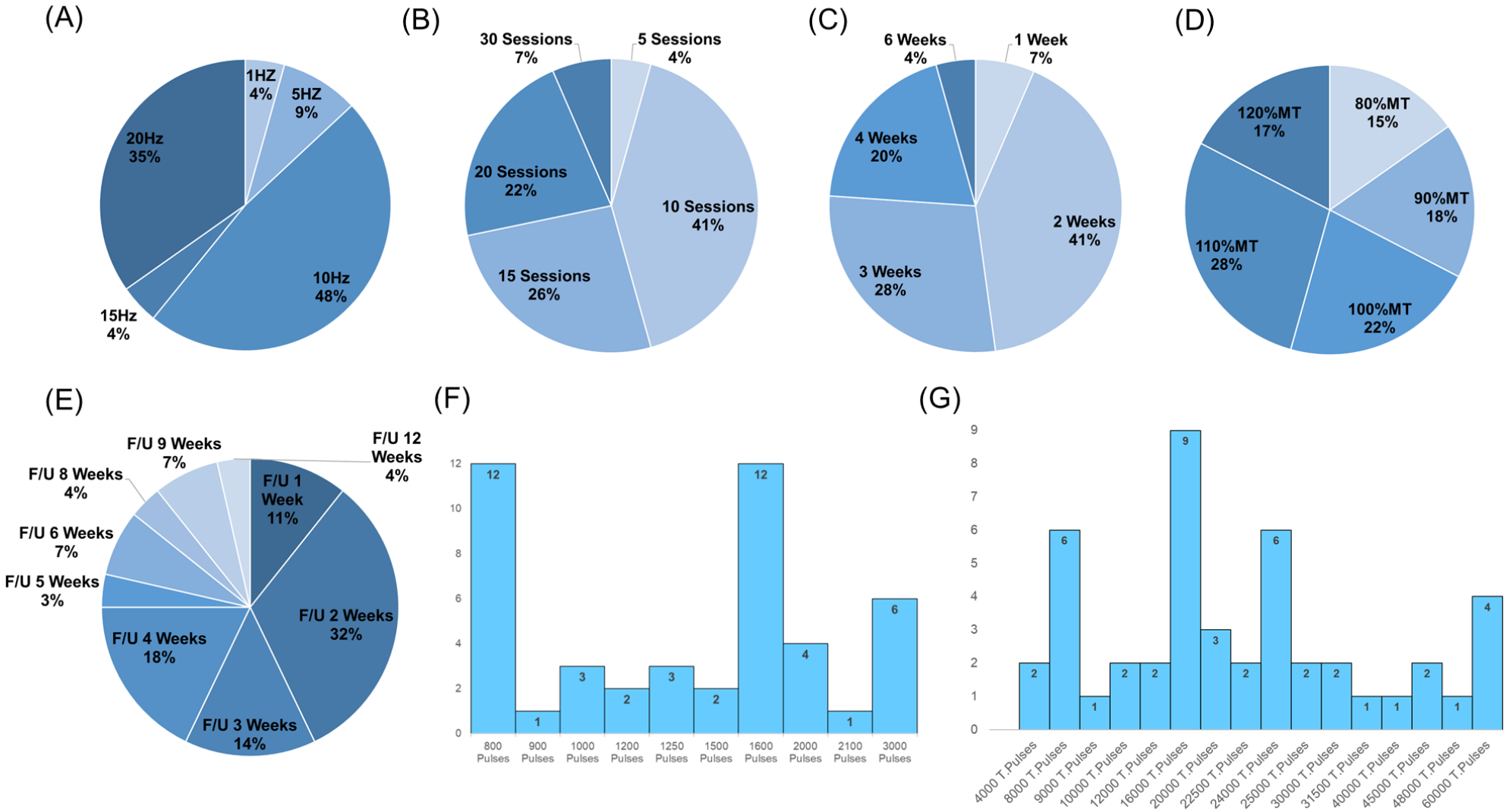
Figure 1. Summary of rTMS protocols and characteristics



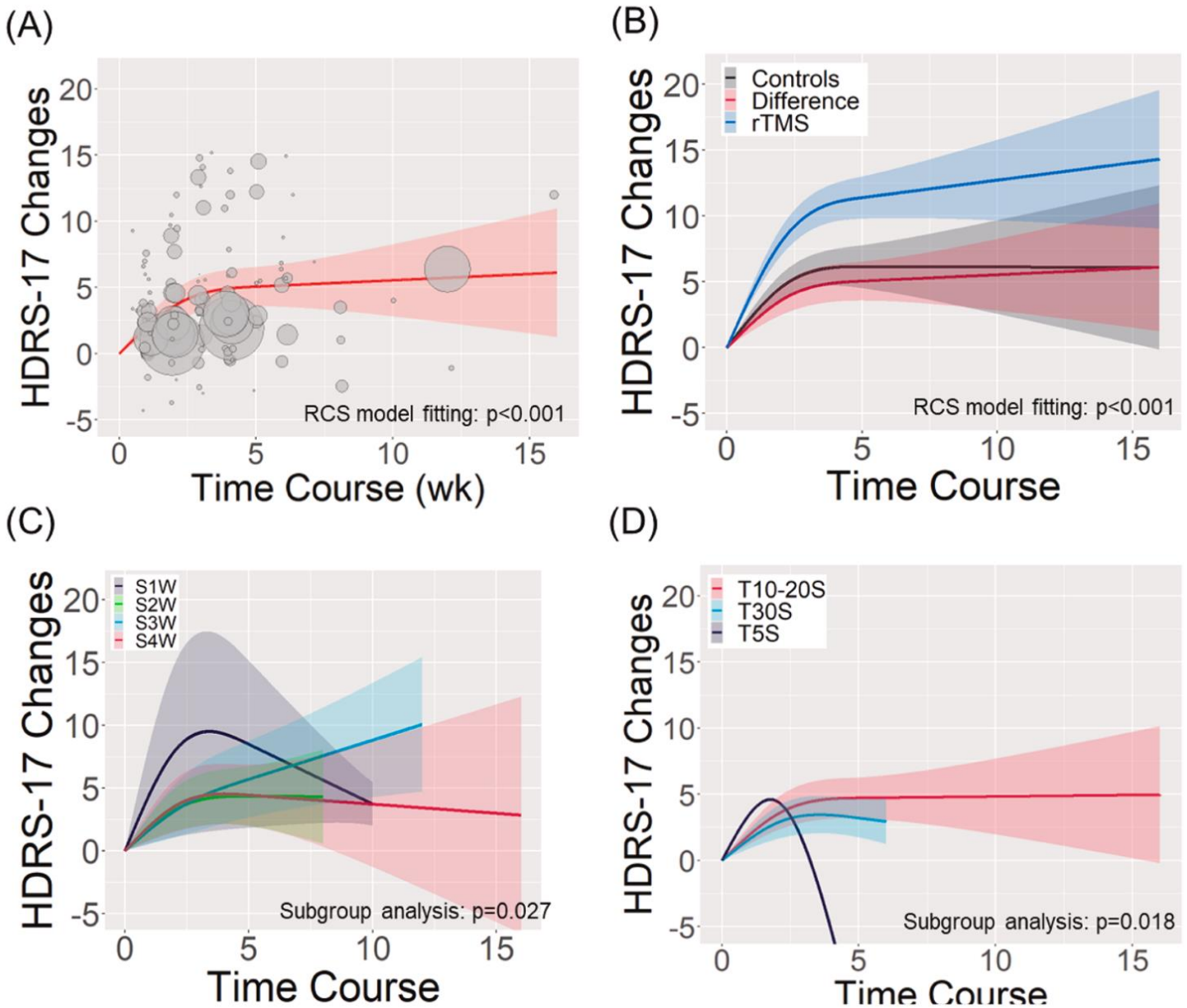


Fig. 2. Trajectory and subgroup analyses. Abbreviations: HDRS-17, 17-item Hamilton Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation; S1W, stimulation for one week; S2W, stimulation for two weeks; S3W, stimulation for 3 weeks; S4W, stimulation for 4 weeks; T10–20S, total 10–20 sessions; T30S, total 30 sessions; T5S, total 5 sessions.

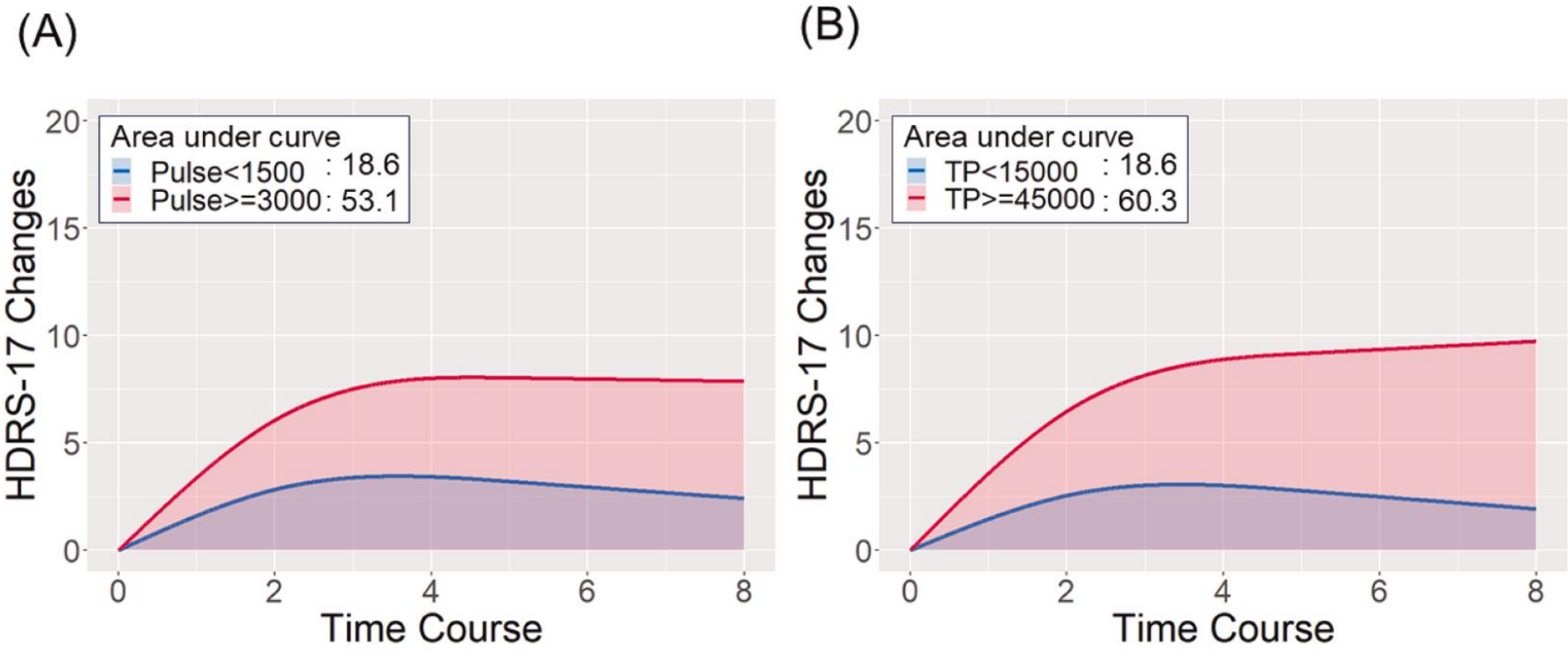


Fig 3. Area under curve of the first 8 weeks. Abbreviation: TP, total pulse.