Effect of rTMS on Parkinson's Cognitive Function: A Systematic Review and Meta-analysis

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Abstract

Background: To evaluate the effects and optimal parameters of repetitive transcranial magnetic stimulation (rTMS) on cognition function of Parkinson's disease (PD) patients and to estimate which cognitive function may obtain more benefits from rTMS.

Method: The articles dealing with rTMS on cognition of PD patients were retrieved from the databases until April 2019. Two researchers selected research papers, evaluated their quality, extracted data, and cross-checked them according to the inclusion and exclusion criteria. The standardized mean differences (SMDs) with 95 % confidence interval (CI) of cognitive outcome for different parameters, scales, and cognitive functions were estimated.

Results: Fourteen studies involving 173 subjects were included in the study. A significant effect size was observed with the mini-mental state examination (MMSE) for the global cognitive outcome based on the evidence of four published articles. Further subtests for different cognitive domains demonstrated prominent effect for the executive function. The significant effect sizes for executive function were found with multiple sessions of high-frequency rTMS over frontal cortex, especially over dorsolateral prefrontal cortex (DLPFC). All of the other cognitive domains including memory, attention, and language ability did not obtain significant effects.

Conclusions: Multiple sessions of high-requency rTMS over the DLPFC may have positive effect on executive function in PD patients. Further well designed studies with large sample sizes are needed to verify our results and ascertain the long-term effects of rTMS.

Background

Parkinson's disease (PD) is the second largest progressive neurodegenerative disease except Alzheimer's disease (AD). In addition to motor symptoms such as bradykinesia, rigidity, postural instability and gait disturbances, PD patients are usually accompanied by a series of non-motor symptoms (NMS) such as depression, cognitive dysfunction, and autonomic dysfunction [1]. According to epidemiological data, the NMS of PD are common, occur across all stages of PD, are under-reported, and are a key determinant of quality of life [2]. In all NMS, cognitive dysfunction, as the most common and probably most devastating, results in a spectrum of deficits ranging from MCI to severe dementia [3] and can present early in the disease course. A recent review [4] has shown that 21% of their PD sample met criteria for PD-MCI, and 17% had dementia. Nearly 80.0 % of MCI patients eventually develop dementia in the later stages of the disease, and dementia is an important and independent predictor of mortality in patients with PD [5-6]. The forms of cognitive deficit in PD patients vary including executive dysfunction, visual spatial disorder, memory decline, and language dysfunction. Among them, executive function impairment was the most prominent, as a clinical practical multi-center collaborative study [7] found executive dysfunction accounted for 10.1% in PD patients with cognitive deficit. However, the physiological processes mediating cognitive changes are less understood and often overlooked by clinicians, and the underlying pathogenesis and mechanism of cognitive deficit in PD patients is still unclear, but it is closely related to the complex neuropathological

abnormalities of PD [8]. For instance, in PD patients, neurotransmitters in the brain are changed, dopaminergic neurons in the substantia nigra are lost, striatum dopamine is depleted, and the cortical-subcortical dopamine loop between basal ganglia and frontal lobe is significantly damaged [9-10]. Beyond that, the atrophy of the hippocampus and frontal cortex as well as the precipitation of abnormal proteins in PD patients may be factors contributing to cognitive deficit. So far, there is no cure for PD. Traditional treatments such as physical cognitiving exercises, pharmacotherapy, and cognitive therapy are still controversial and need further confirmation. Some of these therapies may cause a series of side effects such as nausea, vomiting and aggravating symptoms of exercise [11]. Therefore, identifying safe therapies to alleviate symptoms remains a priority.

In recent years, according to the reporting guidelines established by a group of European experts on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS), based on evidence published until 2018, rTMS are recommended as a potential therapeutic tool for various neurological and psychiatric disorders [12]. rTMS is a painless, noninvasive, well-tolerated technique of brain stimulation based on the theory of electromagnetic induction [13]. It induces currents in local areas of the cerebral cortex through rapidly changing magnetic fields to depolarize the synaptic cells of central nervous system and produce the activity of synaptic terminals, thus causing a series of brain metabolic changes in neuronal potential activity and other physiological functional responses [14]. Long term of rTMS has cumulative effect on the brain, some of which might depend on long-term potentiation (LTP)/longterm depression (LTD)-like changes in synaptic connections between cortical neurons[15], which has been reported by some studies in various neurological, psychiatric, and neuropsychiatric diseases and even in healthy controls [16-19]. The nature of the after-effects of rTMS depends on the stimulation site, pulse number, stimulation intensity, frequency, and the number of treatment sessions [15]. For example, stimulation at frequencies higher than 1 Hz tends to increase rather than decrease cortical excitability [20]. However, due to the lack of understanding on the mechanism of sustained repair of cortical excitability caused by stimulation, and the variability of the within-subject and between-subject induced by rTMS, there is no consensus on rTMS parameters and overall efficacy.

Six reviews/meta-analyses were published to summarize the clinical research results in recent years. Two reviews were published by Anderkova et al. In 2014, their study[21] preliminarily summarized the application of rTMS on cognitive impairment in PD patients, AD patients, and MCI patients from a clinical perspective, which contained its after-effects and inter-individual variability in their magnitude, discrepancies in stimulation protocols and study designs, varied selection of the specific stimulated areas and control procedures, and neuropsychological methods for assessment of after-effects. In 2017, their second study [22] reviewed the therapeutic potential of non-invasive stimulation and included both rTMS and transcranial direct current stimulation (tDCS) on depression and NMS in PD patients. The results were quite preliminary but hopeful, showing rTMS had some positive effects on depressive symptoms and cognitive impairment in PD patients. Also in 2017, Dinkelbach's review [23] summarized the importance of rTMS stimulation sites, considering dorsolateral prefrontal lobe (DLPFC) as a crossroads of depression and cognitive function. Randver's review, [24] in 2018, pooled available literature on the therapeutic usage of rTMS on NMS of PD associated with the DLPFC (i.e. mood disturbance and cognitive impairment), which showed high-

frequency rTMS was beneficial for PD-related depression, but the availability of reducing PD-related cognitive impairment has remained uncertain. The above review yielded preliminary results, but there are still obvious controversies and lack of specific data support. Also in 2017, Lawrence et al[25] performed a detailed analysis of rTMS on varies cognitive domains in PD, which only included three articles, and showed a negative outcome. In the same year, in the study of GoodWill et al [26] no effect for stimulation parameters on cognitive function was observed, based on the evidence of 5 published articles. Although quantitative analysis based on objective data is carried out in the above two articles, there is no further subgroup analysis for treatment parameters. Subsequently, in 2018, Cohen et al.[27] and Buard et al. [28] both published studies about the effects of rTMS treatment on cognitive function of PD patients. Therefore, the purpose of this study was to provide an objective and comprehensive analysis that whether rTMS treatment was effective on cognitive function of PD patients which cognitive domain obtained more from rTMS stimulation and which rTMS parameters are the most appropriate.

Method

The meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.

Search strategy

We performed the meta-analysis with the data from the PubMed, Cochrane Library, Embase, Sciencedirect, and Web of science published before April 2019. In order to collect the literature comprehensively, a wide range of terms were used: “rTMS” or “TMS” or “magnetic stimulation” or ‘repetitive transcranial magnetic stimulation’, “cognitive” or “cognition” or “MCI” or “mild-cognitive impairment” or “neurodegenerative”, and “Parkinson” or “PD”.

Inclusion and exclusion criteria

The included studies strictly meet the following inclusion criteria: application of rTMS, involvement of PD patients, measurement of the cognitive function (i.e. memory, execution, attention, language functions, and global cognitive function), published in English. Exclusion criteria: multiple combined interventions, insufficient data, no standardized cognitive outcome, study protocol, case-report study. In order to include all relevant articles more broadly, the design of the test was not limited. Randomized controlled trials (RCT), crossover trials, and self-controlled trials were included in the search.

Study quality

The research publication evaluation process was carried out by the first and second authors of the study, and the evaluation criteria was based on the improved evaluation scale of Moher et al. It mainly included the following evaluation items; 1) whether the experimental design was randomized; 2) whether the blind method was adopted and the type of the blind method was recorded in detail; 3) During the experiment, whether the subjects drop out, if so, whether the number of drop out is recorded in detail; 4) whether the detailed basic information of the subjects was included; 5) whether the experiment was a comparison

between the control group and the experimental group; and 6) whether any adverse reactions were reported, and if any, the number of adverse reactions, the type, and severity of adverse reactions were described in the article.

Data extraction

Two experienced reviewers independently evaluated the studies based on the inclusion/exclusion criteria. Any disagreement was resolved through discussion and consultation with a third reviewer. The detailed basic information was extracted which included the first author, release year, intervention method, the course of the disease, number of subjects, and rTMS parameters (Table 1). In order to reduce the heterogeneity produced by different experimental designs including RCT, crossover trials, and self-controlled trials, we only extracted the mean and standard deviations (SD) of the cognitive scale data before and after rTMS treatment. If the standard error of the mean (SEM) was provided, it was converted to SD by using the formula of SD = SEM×. Due to multiple domains of the cognitive function, a single scale to detect rTMS treatment for cognition may not be meaningful. So based on the existing classification and cognitive scales mentioned in the included studies, four categories involving executive function, memory, attention, as well as language function were analyzed in this meta-analysis. The response time and accuracy of the different cognitive tasks was recorded to combine the results to reflect the therapeutic effect of rTMS. In addition, in order to avoid the heterogeneity caused by the diversity of the scale, we tried to unify the scale in the same cognitive field when multiple cognitive tests was applied in the study.

Statistical analysis

The meta-analysis was conducted by using RevMan 5.3 software provided by Cochrane collaboration (London, UK). The standardized mean difference (SMD) and its 95% confidence interval were selected to display the combined results. The heterogeneity was tested by using the Cochran's Q statistics and I^2 test. If the I^2 value was greater than 50%, the random effect model was used for the analysis. Otherwise a fixed model was used. Moreover, by examining the data extraction method and the raw data included in the study, by analyzing the clinical intervention measures and experimental design, and by using sensitivity analysis as well as other methods to find the cause of heterogeneity. We used the inverted funnel chart to assess the presence of possible publication bias. In addition, some subgroup analyses were conducted to assess the influence of moderator variables of rTMS on cognitive function. Comparison of outcome variables used a $P < 0.05$ value for statistical significance.

Result

Characteristics of the included research literature

The computer retrieved 208 articles. After reading the title and abstract and excluding duplicate documents, 14 documents were finally left that met the criteria. The detailed article screening process was shown in Figure 1. A total of six parallel design experiments, five cross-design experiments, and three self-control design experiments were included in this study. Seven articles were evaluated for overall cognitive function, 13 articles for different cognitive domains (e.g., executive function, memory, attention, and language

function). All articles contain data on immediate efficacy after treatment, while only three articles have follow-up data.

Characteristics of the patients with PD

A total of 249 PD patients were enrolled in the 14 studies. But, in our meta-analysis, only the data of patients from the real rTMS group was extracted. Therefore, only 173 PD patients were included in our study. A total of 70 subjects suffered from depression. Three articles included a total of 46 patients with idiopathic PD. Most studies had no detailed information on the patient's motor syndrome such as tremor, Bradykinesia, or posture gait abnormalities. Six patients suffered from dementia. The average age of the subjects included in 12 articles is over 60 years old, the average age of the subjects included in one article is over 70 years old and another article does not provide the average age of the subjects. The mean disease duration of almost all patients was more than five years, and even the mean disease duration of individual patients was more than 10 years. As shown in Table 1. Most patients have stable medication for a period of time before and during treatment, but lack of detailed information about specific drugs.

Document quality evaluation result

Randomized allocation was used in 11 studies, but detailed distribution method was not mentioned in the other three studies. Seven articles were double-blinded, four studies were single-blinded, and three studies did not report blind-related information which was defined as an unclear blinded method. Four studies documented the dropout of patients in the middle of the study, and the remaining ten studies did not report any dropouts if they occurred or not. Almost all articles contained complete patient information such as age, duration of illness, and education level. Adverse reactions were reported in eight studies, two of which definitely reported the number among, mild headache was the main side effect, and the rest did not report the number. No adverse reactions were reported in the remaining six studies. No serious side effects were reported in all articles. (Table 2).

Efficacy evaluation of rTMS on overall cognitive function

Seven studies, which included 96 subjects, evaluated the efficacy of rTMS on the overall cognitive function. Fixed effect mode combined results showed that rTMS treatment improved cognitive function but did not achieve significant results (SMD = 0.23, 95 % CI, -0.06 to 0.51, P = 0.12) (Figure 2a). Figure 2a indicated that the inconsistency of the overall cognitive scale may lead to deviations in results. Thus, the cognitive scales were divided into the Mattis Dementia Rating Scale (DRS) group, the Mini-Mental State Examination (MMSE) group, and the Montreal Cognitive Assessment (MoCA)..

Different scale subgroup results

The scale subgroup analysis with random effect model showed that the MMSE group had significant results without heterogeneity (SMD = 0.49, 95 % CI, 0.06 to 0.92, P = 0.02). Figure 2b showed the results of the two sets of scales which were distinctly different indicating the choice of the scale may result in a certain deviation.

rTMS treatment for different cognitive areas

We refined the cognitive domains into four parts which included executive function, memory, attention function, and language function. Among them, 11 studies related to executive function included 166 patients; eight studies related to memory included 134 patients; six studies related to attention included 116 patients; and five studies related to language function included 95 patients. The fixed effect model combined results showed a significant improvement on executive function after rTMS（SMD = 0.25, 95 % CI, 0.04 to 0.47, P = 0.02), but no significant results were found in other cognitive domains. The result of the funnel plot (Figure 3a) showed that the left and right were basically symmetrical indicating there was no or slight publication bias. The result was shown in Figure 3b.

Subgroup results on the executive function

Because there was almost no heterogeneity in the group of different cognitive domains, we only performed a subgroup analysis of the executive function, mainly based on frequency, the treatment site, and the session of treatments. Generally speaking, the frequency was divided into high-frequency (> 1.0 Hz) and low-frequency (≤ 1.0 Hz). Sensitivity analysis found that, after removing low-frequency stimulus document, the combined results of high-frequency stimulation still had a significant effect (SMD=0.23（95 % CI（0.01 to 0.46（p = 0.04), as shown in Figure 4. Based on the intimate connection between the frontal area and cognitive function, the treatment site was divided into two groups: the frontal region and other regions. The fixed effect model combined results showed the frontal region group had significant results after rTMS treatment when compared to other regions group (SMD = 0.40 95 % CI, 0.11 to 0.68, P = 0.006), as shown in Figure 5a. In the frontal region, the DLPFC, as the higher cognitive nerve center, is closely related to executive function. In order to get more accurate brain localization, we divided the prefrontal cortex into the DLPFC group and other frontal region group. The fixed effect model combined results showed compared to other frontal regions group, the DLPFC group had more significant results (SMD = 0.36, 95 % CI, 0.04 to 0.68, P = 0.03). Details are shown in Figure 5b. The session of treatments can be divided into two groups: single session treatment and multiple session treatments. The combined results using a fixed model showed multiple session treatments were significantly effective after rTMS treatment（SMD = 0.33, 95 % CI, 0.07 to 0.59, P = 0.01). Details are shown in Figure 6a. In addition, the result of multiple sessions was still significant when only the studies on DLPFC were used (SMD = 0.41, 95 % CI, 0.07 to 0.76, P = 0.02). Details are shown in Figure 6b.

Discussion

In this study, we quantitatively tested the efficacy of rTMS on cognitive functions of PD patients. On the whole, the results of the published works showed positive effect of rTMS, mainly in specific tasks MMSE, which had a significant performance, suggesting the effect of rTMS on patients was associated to task-specific cognitive improvement. Moreover, the stratified results showed the high frequency rTMS stimulation over the DLPFC for multiple sessions had a significant performance on executive function of PD patients, but in other cognitive domains, no positive performance was found.

In 2017, another meta-alalysis of Lawrence et al. [18] showed that cognitive function did not appear to be improved after rTMS. But, this article only enrolled 3 rTMS studies which investigated different cognitive fuctions, involving global cognition, executive function, and attention respectively. Besides, the subgroup analysis was also performed, in which 1 study was included for global cognition, 2 studies for executive function, and 1 study for attention. In order to get preliminary results of rTMS trials in cognition in PD, more detailed exploration of this therapeutic technique should be required. Also GoodWill et al showed a negative result, based on the evidence of 5 published articles. There is no reasonable refinement of the cognitive domain, and the integration of executive function and psychomotor speed is analyzed as global cognition. The results of these measures should be taken with caution. In our study, 14 studies showed that rTMS treatment played a positive role in the improvement of cognitive function which was similar to previous reviews of Anderkova et al. [22] and Dinkelbach et al[23] in 2017. In fact, the efficacy of rTMS on cognition was reported in other neuropsychiatric disorders meta-analysis, such as, in both dementia [29] and schizophrenia [16] studies. Subgroup results of overall cognitive function showed cognitive improvement in the MMSE group was significantly better than that in the DRS group and the MoCA group, revealed that the specificity of the task results deviation in outcomes. Because only one article used MOCA scale, in order to avoid the result deviation caused by small samples, only MMSE scale and DRS scale were discussed. The MMSE scale is divided into 10 aspects, including orientation, instant memory, attention and computational power, delayed recall, object naming, language retelling, and speech comprehension. From the design of the content of the MMSE scale, it contains a large proportion of the evaluation of the orientation force (10/30 points). The DRS scale contains five factors: attention, start and hold, concept formation, structure, and memory. From the content design of the scale, the concept formation accounts for a large proportion (39/144 points). Each global cognitive scale has slightly laterality for distinct cognitive field. The complaints of typical PD-MCI patients generally include slower work, decreased concentration, and vocabulary search barrier. The most prominent of the damaged cognitive domains found in PD-MCI patients is the ability to executive functions, attention, orientation, etc. [4]. In addition, DRS scores are significantly affected by age and education level, while MMSE is not directly related to these factors. Indeed, DRS is generally more sensitive and specific for general cognitive impairment assessment than MMSE. Even Monsch et al. [30] found the DRS is a clinically valid psychometric test for the detection of dementia patients, in which the Memory and Initiation/Perseveration subscales are its best discriminative indexes. But our study included PD patients with varying degrees of motor symptoms and uncertain medications, even some of which accompanied with moderate and severe depression. The crossover of complex symptoms as an unavoidable factor may affect the results. But, the low sensitivity of MMSE scale

may lead to the deviation to the result and the impact of low sample size (only 4 articles for MMSE) also should not be ignored. Therefore, this result still needs to be treated with caution. The Movement Disorder Society Task Force recommended a series of neurocognitive scales to define PD-MCI [31], but the number of scales involved is too large to conducive to rapid screening. Ideal PD cognitive function evaluation tools should comform to the following：1. Covering subcortical and cortical dementia detection items. 2. High sensitivity and specificity are conducive to early diagnosis and differential diagnosis. 3. The relative independence of the assessments in each cognitive area makes it easier for clinicians to distinguish .4. Low impact of exercise symptoms of PD on detection. 5. Reasonable test time and very low fatigue effect.

Subgroup results based on different cognitive domains showed significant improvement on executive function of PD patients after rTMS, especially when high-frequency rTMS stimulation located in the DLPFC for multiple sessions. Similar results have been reported in previous studies. For example, Mogg's study found that a 10 days of high rTMS posited on DLPFC had some improvement on the executive function of schizophrenia. In addition, Moser et al. [32] performed rTMS stimulation (20.0 Hz and 80 % MT) over DLPFC in 19 patients with dysfunction and showed that the TMT connection test and SCWT scores of the rTMS group had significant improvement. Executive functions include planning, organization, and goal-directed behavioral adjustments. The damage of executive function reflects the damage to the frontal lobes of the brain, particularly the DLPFC, which ultimately leads to the degradation of the nigrostriatal dopamine pathway and the midbrain pathway [33]. Low dopaminergic status, such as before dopaminergic therapy, after the removal of levodopa or other dopaminergic drugs, and sudden drug reduction, can cause disorders in executive function which result in reduced flexibility of mental activity [34]. The causes of cognitive impairment in non-demented PD generally include changes in dopaminergic and cholinergic neurotransmitters, neuropathological changes in the limbic system, cortex and other systems, Lewy bodies, neurofibrillary tangles, and cerebrovascular diseases [35]. One previous study [36] found that rTMS stimulated the frontal cortex to regulate the dopamine system causing an increase in dopamine release in the basal ganglia which in turn improves the executive function of PD patients. Beyond that, executive function, as a process of higher cognitive function, is usually closely related to the cooperation of multiple brain regions. It is probable that stimulation of the DLPFC not only impacts cortical excitability but also within the stimulated cortex that has been engaged in the cognitive task which leads to excitability changes of the whole circuitry. That is, the associative basal ganglia-thalamo-cortical loop is interconnected with the stimulated area [37-38].

An important consideration is the parameters of rTMS are related to effects on cognitive rehabilitation of PD with cognitive deficits. Frequency is one of the most important parameters of rTMS. High frequency can change local neuronal activity and improve the excitability of cerebral cortex. In contrast, low frequency stimulation can inhibit local neuronal activity and reduce the excitability of cerebral cortex. In addition, different frequencies of stimulation may contribute to distinct effects on cortical metabolism and cerebral blood flow, For example, high frequency may lead to increased local metabolism, while low frequency may lead to decreased metabolism. As Conca et al. [39] reported, rTMS can change the frontal cerebral blood flow and brain metabolism in patients with depression, thereby, improving depressive symptoms. Our results suggest that high frequency stimuli are more effective on cognition, and most of the literature we

included tended to use high frequency. At the same time, there have been numerous reports in other psychiatric literature about the efficacy of high frequency for cognitive impairment. For the session of rTMS treatments, a large number of meta-analyses from previous studies have found that treatment sessions have better results within certain limits [40-41]. In general, rTMS generates local nerves stimulated by micro-currents which affects multi-site functions through the connection and interaction between neural networks. The effect of a single session is limited and hardly long lasting. Multiple sessions results in cumulative and long term benefits. However, excessive stimulations can lead to headaches, nausea, epilepsy, mental disorders and other side effects. Our results showed that the effect of a single session is not significant, but the specific parameters require further experimental support.

Other cognitive domains such as memory, language, and attention have not found significant results. Previous studies of other mental illnesses have shown that rTMS stimulation played on the forehead area significantly improved the memory function of patients, but it has not been found in this study which may be related to the subjects included in the study. Clinical manifestations of PD patients were heterogeneous and included memory impairment and non-memory impairment with single lesions and composite lesions. Although some patients showed more memory or cortical injury, in general, single non-memory damage accounts for the subject. Frontal cortical function or executive function is the most common impaired domain followed by impaired memory function [42-43]. Another PD-MCI multi-center study showed the similar result that executive function disorders accounted for a large proportion of PD patients with cognitive impairment [7]. Second, the duration of the subjects included in our study was more than five years or even longer. Many patients may be in moderate cognitive impairment, and the effect of rTMS is not obvious compared to the MCI. Therefore, although the structural anatomy of memory is in the dorsolateral prefrontal cortex, the effect is not significant. For language function, from the past research, the anatomical structure of language function was mainly located in the lower part of the frontal gyrus [44-45]. Some imaging studies [46] have even found that language dysfunction is related to temporal lobe and language hemispheres. In addition, the brain regions related to attention are mainly located in parietal and temporal lobes. In the past studies, there have been a lot of similar reports [47-48] and the damage of the parietal structure leads to visual neglect [49]. Hilgetag et al. [50] also found that the patient's visual attention was improved by stimulating the lateral parietal lobe through rTMS. However, most of the stimuli sites included in their study were located in the prefrontal lobe which may not lead to a corresponding improvement in language and attention function after stimulation. Of course, the completion of any cognitive task is not the result of a single brain region but the product of multiple brain regions. However, the application of accurate rTMS positioning is still a key task in improving different cognitive functions.

There are some shortcomings in this study. First, although 14 articles were included, the published studies showed a great variability in demographic characteristics of subjects, simulation parameters, study protocol designs, and outcome measures. Second, some of the PD patients even suffered from moderate or major depression, and the intricate intertwined disorder was an important factor influencing the outcome. Third, there are many scales for the measurement of cognitive function, but there is no uniform standard in the world. The poor sensitivity and specificity of some scales may lead to some deviations. Fourth, since the p-values were not corrected for multiple comparisons, it may have an impact on the results. Finally, the

included studies relatively lacked of the follow-up period, so we could not evaluate the sustainability of its long-term differentiation. Whether the curative effects of rTMS could be sustained for a long time is still unknown. Further studies with large sample size of experiments involving long-term follow-up effect after treatment are needed to increase the reliability that rTMS performs on cognitive impairment.

Conclusion

This study shows rTMS therapy may have a promising effective way of treatment on the cognitive impairment of PD patients. In particular, executive function of PD patients who had benefit with high-frequency rTMS stimulation located in the DLPFC for multiple sessions. In the future, we hope that there will be more experimental design which is rigorous, and have large sample experiments to support our results.

Abbreviations

rTMS: repetitive transcranial magnetic stimulation

PD: Parkinson's disease

SMD: standardized mean differences

CI: confidence interval

DLPFC: dorsolateral prefrontal cortex

AD: Alzheimer's disease

NMS: non-motor symptoms

tDCS: direct current stimulation

RCT: randomized controlled trials

DRS: Mattis Dementia Rating Scale

MMSE: Mini-Mental State Examination

MoCA: Montreal Cognitive Assessment

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. All authors declared no competing interests.

Availability of data and materials

Data generated during this study are included in this published article.

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Author contributions

JY and GZW screened the literature and extracted the data. GZW and MM completed data sorting and analysis. JY wrote the manuscript. MM and HL contributed to the revision of the manuscript. The corresponding author MQW contributed to the overall of the article.

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Tables

Table 1. Characteristics of Included Studies

Author/ Year	Subject	Age	Duration	Stimulation Parameters			
				Position	Session	Frequency	Intensity
Kimura 2011	12	69.2	8.5	SMA	4	0.2 Hz	
Toshiaki 2009	6	66.8	7.17	Frontal region	12	0.2 Hz	120% RMT
Pal 2010	12	68.5	6	Left DLPFC	10	5 Hz	90% RMT
Cardoso 2007	11	67.0	11	Left DLPFC	12	5 Hz	120% RMT
Epstein 2007	14	62.0		Left DLPFC	10	10 Hz	110% RMT
edlkov 2009	10	63.7	7.8	Left PMd	1	10 Hz	100% RMT
				DLPFC	1	10 Hz	100% RMT
				OCO	1	10 Hz	100% RMT
Dagan 2017	7	74.6	10	mPFC	16	10 Hz	100% RMT
Chang 2017	16	63.8	9.1	M1-LL	5	10 Hz	90% RMT
Cohen 2018	21	64.4	4.7	M1+PFC	24	1 Hz+10 Hz	110%+100% RMT
Boggio 2005	13	65.2	6.7	Left DLPFC	10	15 Hz	110% RMT
Buard 2018	22			Bilateral DLPFC	10	20 Hz	
Grovnalova 2011	10	66.0	5.4	Left and right inferior frontal gyri	1	25 Hz	80% RMT
Grovnalova 2012	10	66.0	5.4	Left DLPFC	4	25 Hz	80% RMT
				Right DLPFC	4	25 Hz	80% RMT
Benninger 2009	9	62.6		Left M1	1	50 Hz	60% RMT

Exp: Experimental Group; Ctr: Control Group; SMA: Supplementary Motor Area; DLPFC: Dorsal Lateral Prefrontal Cortex; PFC: Prefrontal Cortex; M1: Primary Motor Cortex; mPFC: medial

Prefrontal Cortex; PMd: Dorsal Premotor Cortex; OCO: Occipital Cortex; M1-LL; Primary motor cortex of the lower leg

Table 2. Quality assessment of included literatures. yes*= Unclear the exact number

Study	Randomization	Blinding	Dropout	Description of basic features	Control study	Adverse events
Boggio2005	yes	double	0	yes	yes	0
Cardoso2007	yes	double	0	yes	yes	yes*
Kimura2011	unclear	double	0	yes	yes	0
Srovnalova2011	yes	single	0	yes	yes	2
Srovnalova2012	yes	single	0	yes	yes	2
Sedlkov2009	yes	single	0	yes	yes	0
Pal2010	yes	double	0	yes	yes	yes*
Benninger2009	unclear	unclear	1	yes	no	0
Epstein2007	unclear	unclear	2	yes	no	0
Buard2018	yes	double	2	yes	yes	yes*
Toshiaki2009	yes	unclear	0	yes	no	0
Dagan2017	yes	single	2	yes	yes	yes*
Cohen2018	yes	double	0	yes	yes	yes*
Chang2017	yes	double	0	yes	yes	yes*

Figures

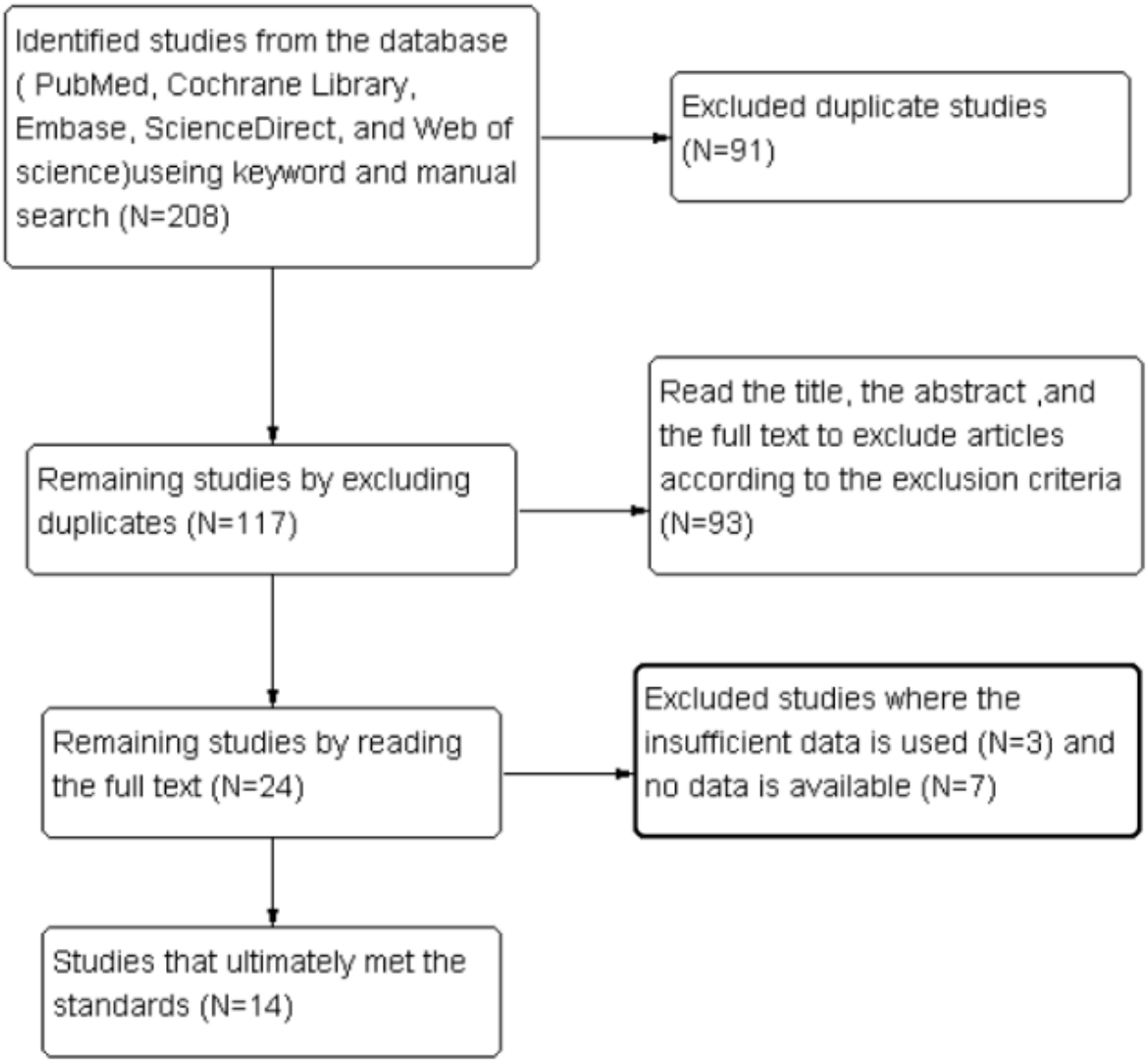
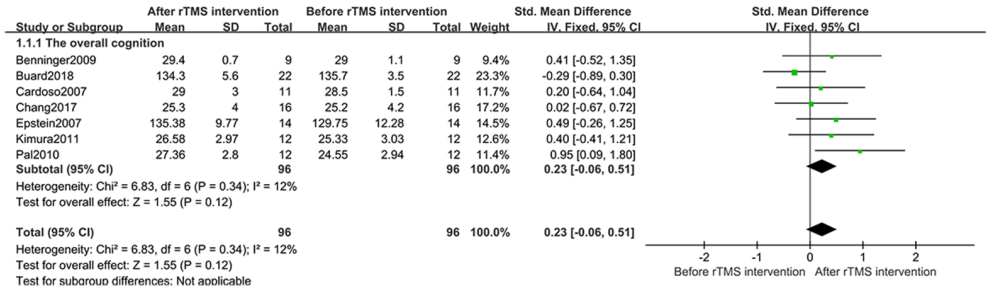
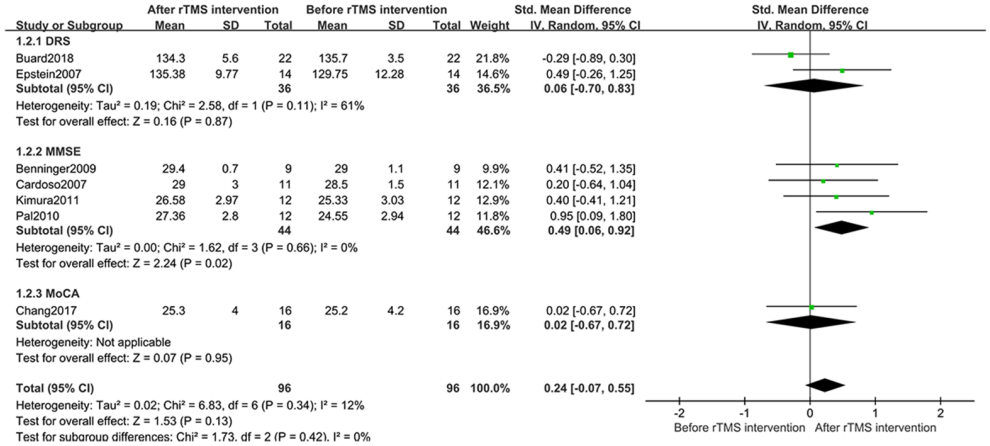


Figure 1

Study screening flow char.



a



b

Figure 2

a. Overall cognitive efficacy after rTMS treatment, b. Overall cognitive different scales subgroup efficacy after rTMS treatment.

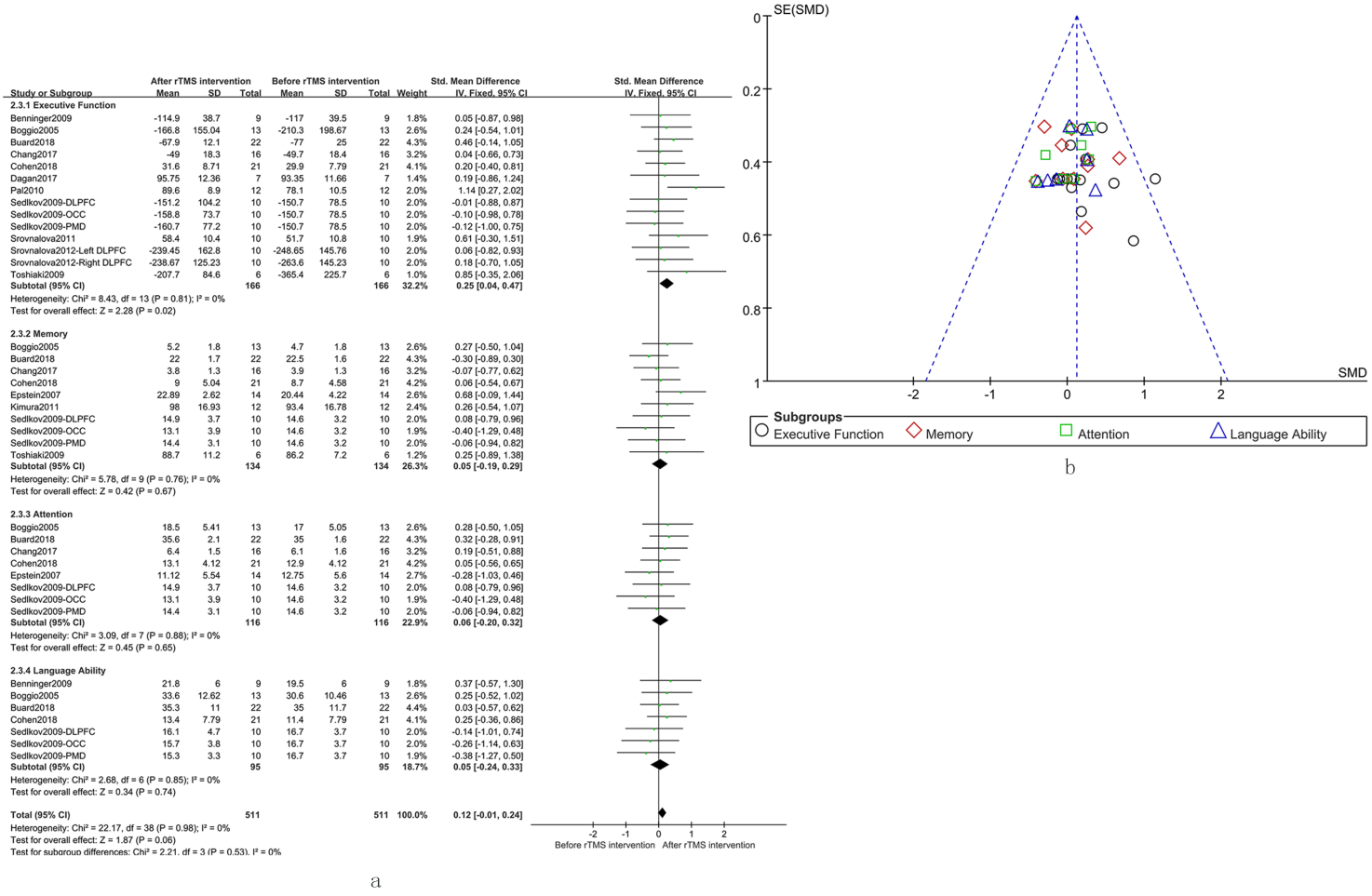


Figure 3

a. Therapeutic effects of different cognitive domains after rTMS treatment, b. Publication biased funnel plots in different cognitive domains.

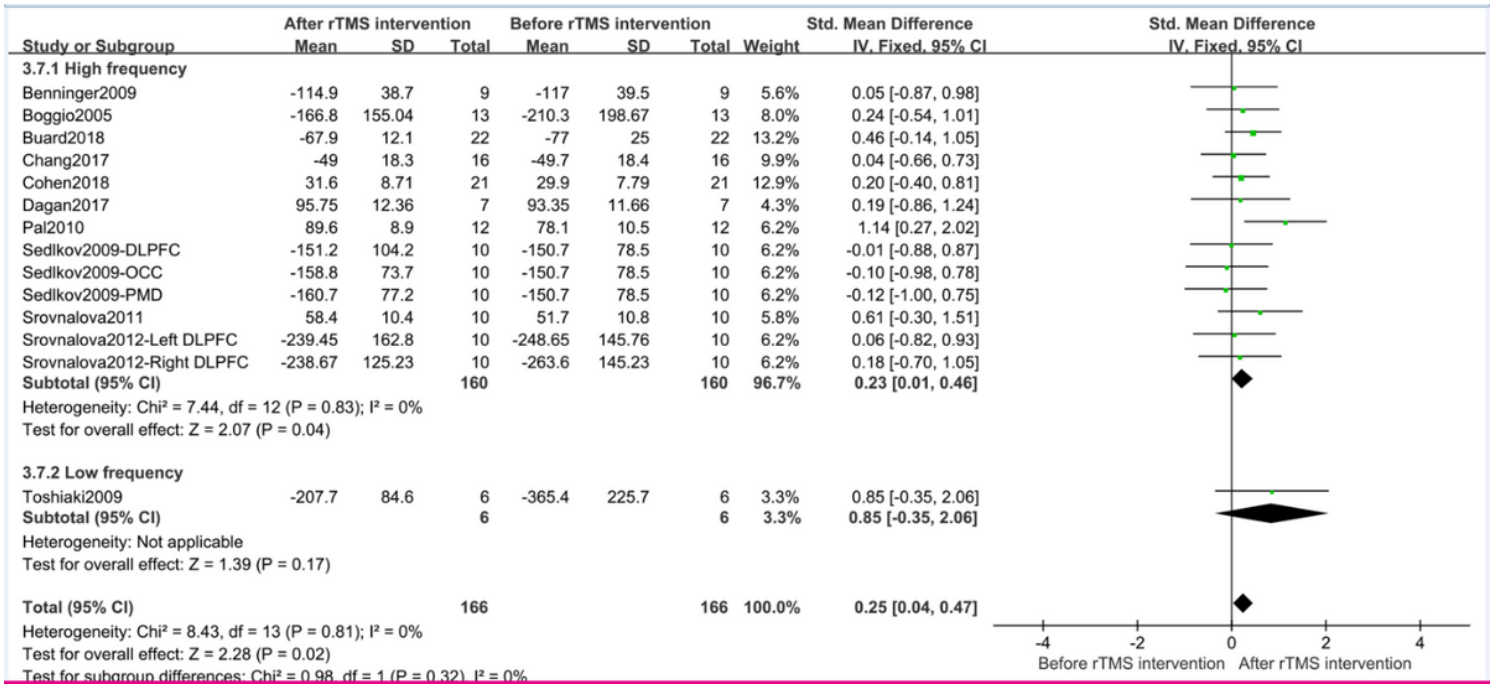
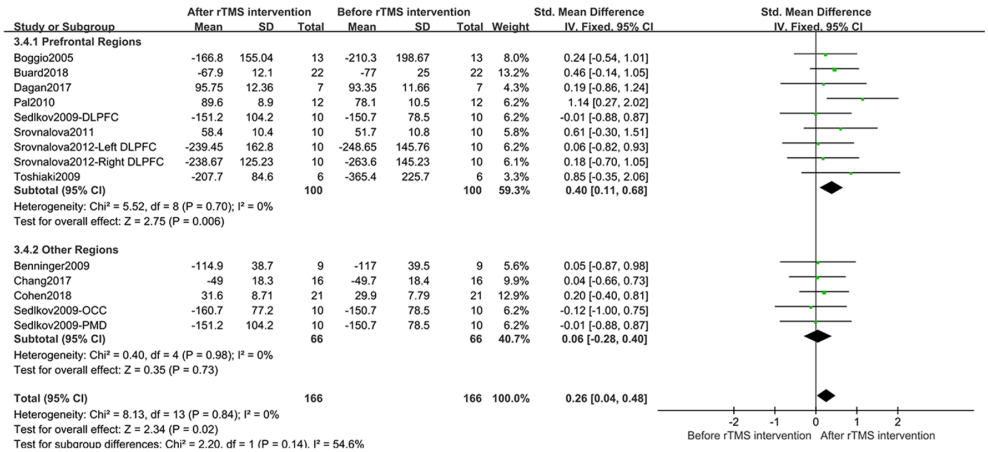
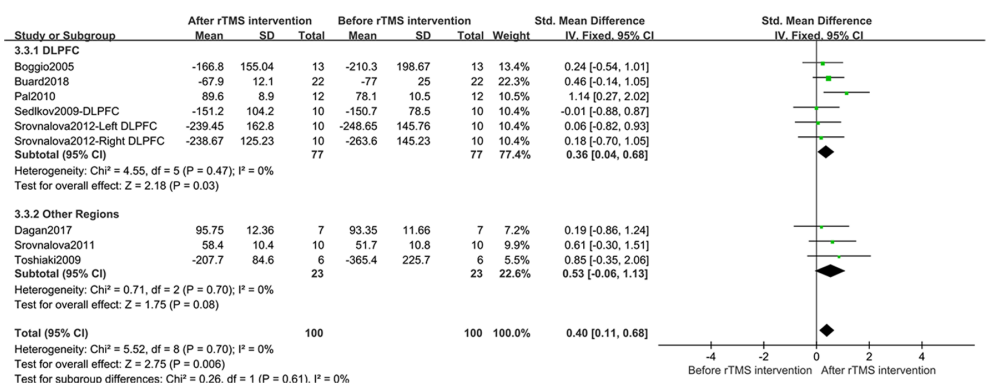


Figure 4

Stimulation frequency subgroup results after rTMS on executive function.



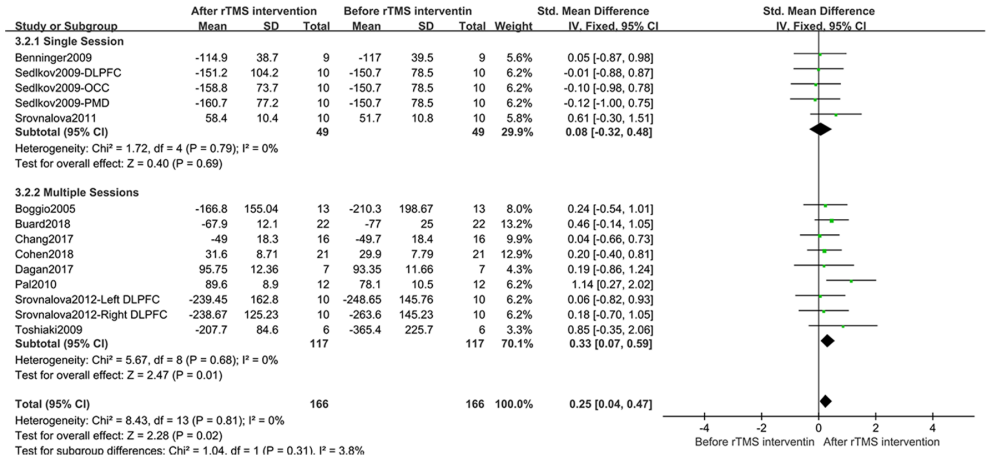
a



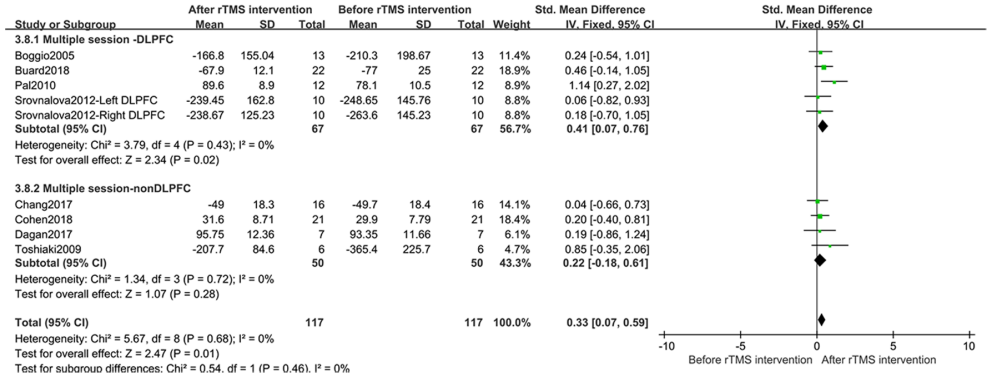
b

Figure 5

a. Stimulation site subgroup (the frontal region vs other regions) results after rTMS on executive function, 5b.Stimulation site subgroup (the DLPFC group vs other frontal regions group) results after rTMS on executive function.



a



b

Figure 6

a. Stimulation session subgroup results after rTMS on executive function, b. Stimulation site subgroup (the DLPFC group vs other regions group) after multiple sessions rTMS on executive function.

Supplementary Files

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