Effect of rTMS on Parkinson's Cognitive Deficit: 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 improvement of Parkinson’s disease (PD) patients with cognitive deficit and to estimate which cognitive function may obtain more benefit from rTMS.

Method: The articles dealing with rTMS on cognitive deficit of PD patients were retrieved from the databases until December 2018. 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 163 subjects were included in the study. A significant effect size was observed for the mini-mental state examination (MMSE) global cognitive outcome. Further subtests for different cognitive domains demonstrated prominent effect for the executive function. The significant effect sizes were respectively found with multiple sessions of high-frequency rTMS over frontal cortex, especially with over dorsolateral prefrontal cortex (DLPFC), based on subgroup analysis of the executive function. All of the other cognitive domains including working memory, attention, and language ability did not obtain significant effects.

Conclusions: Multiple sessions of high frequency rTMS over the DLPFC may have positive effect on executive function in PD patients with cognitive deficit. 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 neurodegenerative disease after Alzheimer’s disease (AD). In addition to motor symptoms such as Bradykinesia, resting tremor, dystonia, and abnormal posture gait, motor symptoms are usually accompanied by a series of non-motor symptoms (NMS) such as depression, cognitive dysfunction, and autonomic dysfunction in PD patients[1]. According to epidemiological data, almost all PD patients have different degrees and types of NMS before or after motor symptoms which cause a significant impact on their quality of life[2]. In all NMS, cognitive deficit has a higher incidence of NMS with an earlier onset [3]. Many PD patients have mild cognitive
impairment (MCI) at the onset of the disease. As a recent review [4] has shown. An average of 27.0 % of non-demented patients in PD patients suffered cognitive decline. Nearly 80.0 % of patients eventually develop dementia in the later stages of the disease, and dementia is an important risk factor associated with PD mortality [5]. The forms of cognitive deficit in PD patients vary and including executive dysfunction, visual spatial disorder, memory decline, and language dysfunction. Among them, executive function impairment was the most prominent. In a clinical practice, multi-center collaborative study, [6] the study found executive dysfunction accounted for 10.1% in PD with cognitive deficit. The underlying pathogenesis and mechanism of cognitive deficit is still unclear, but it is closely related to the complex neuropathological abnormalities of PD[7]. 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. Beyond that, the atrophy of the hippocampus and frontal cortex as well as the precipitation of abnormal proteins may be some of the factors that cause cognitive deficit. To date, clinical research for cognitive therapy of PD patients is insufficient. Traditional treatment has been physical and cognitive exercises, pharmacotherapy, and cognitive therapy. The above methods have no significantly deterministic clinical efficacy, and some of which have a series of side effects such as nausea, vomiting and aggravating symptoms of exercise[8]. So many researchers are looking for newer and better practical treatments. In recent years, non-invasive brain stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS), are used as a potential therapeutic tool and are recommended for the treatment of PD patient. rTMS mainly induces currents in local areas of the cerebral cortex through rapidly changing magnetic fields to depolarize the central nervous synapse cells and creating the synaptic terminal nerve activity, thus causing a series of brain metabolic changes in neuronal potential activity and other physiological functional responses. As rTMS stimulation is administered to the brain, in general, the brain regulates its functions in response to external stimuli. Long-term external stimuli can change the structure of the brain’s nerves reconfiguring it for adaptation to the outside world. This is called as neuroplasticity. At this time, the brain’s synaptic structure and neural network
changes accordingly, eventually changing the corresponding behavior and learning ability as well as playing a certain role in the treatment of damaged brain. The cognitive after effect of rTMS has been reported by many authors in different patient populations including dementia patients, PD patients, and even in healthy controls [9 - 12]. 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 or overall efficacy. One study [13] showed that efficacy of rTMS was closely linked to the stimulation site, pulse number, stimulation intensity, frequency, and the number of treatment sessions.

The debates about the efficacy of rTMS treatment on cognitive function of PD patients has continued. Five 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[14] preliminarily summarized the impact 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[15] 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 [16] summarized the importance of rTMS stimulation sites, considering dorsolateral prefrontal lobe (DLPFC) as a crossroads of depression and cognitive therapy. Randver’s review, [17] in 2018, collected available literature on rTMS in the treatment of NMS of Parkinson’s disease (i.e., emotional and cognitive disorders) associated with DLPFC which showed high-frequency prefrontal rTMS was beneficial for PD-related depression, but the availability of reducing PD-related cognitive impairment has remained uncertain. The above review had preliminary results, but still had obvious disputes and was without specific data support. Also in 2017, Lawrence et al.[18] performed a detailed analysis on rTMS treatment for cognitive domains in patients with PD, which only included three articles, and
showed a negative outcome. In 2018, though, Cohen et al. [19] and Buard et al. [20] 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 deficit 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**

The search criteria for published related clinical studies was publications before December, 2018 and were searched from the following databases: PubMed, Cochrane Library, Embase, ScienceDirect, and Web of science. 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 research studies strictly meet the following inclusion criteria: application of rTMS, involvement of PD patients, measurement of the cognitive domain, published in English. Studies were excluded if there was no data available for the size of the effect size. 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) whether there was an exit in the middle of the experiment, and if so whether the study record the
number of exits 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 above. If any disagreement occurred, it was resolved through discussion and consultation with third-party reviewers. The detailed basic information was extracted which included the first author, release year, intervention method, the course of the disease, number of subjects, treatment site, 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 deviation (SEM) of the mean was provided, it was convert to a standard deviation (SD) by using the formula of $SD = SEM \times$. The response time and accuracy of the different cognitive tasks was recorded to combine the results to reflect the therapeutic effect of rTMS.

Table 1. Characteristics of Included Studies
| Author/Year | Subject | Age | Duration | Position | Session | Frequency |
|------------|---------|-----|----------|----------|---------|-----------|
| 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 |
| Pal 2010 | 12 | 68.5 | 6 | Left DLPFC | 10 | 5 Hz |
| Cardoso 2007 | 11 | 67.0 | 11 | Left DLPFC | 12 | 5 Hz |
| Epstein 2007 | 14 | 62.0 | | Left DLPFC | 10 | 10 Hz |
| Sedlko 2009 | 10 | 63.7 | 7.8 | Left PMd | 1 | 10 Hz |
| | | | | DLPFC | 1 | 10 Hz |
| | | | | OCO | 1 | 10 Hz |
| Dagan 2017 | 7 | 74.6 | 10 | mPFC | 16 | 10 Hz |
| Chang 2017 | 16 | 63.8 | 9.1 | M1-LL | 5 | 10 Hz |
| Cohen 2018 | 21 | 64.4 | 4.7 | M1+PFC | 24 | 1 Hz+10 Hz |
| Boggio 2005 | 13 | 65.2 | 6.7 | Left DLPFC | 10 | 15 Hz |
| Buard 2018 | 22 | | | Bilateral DLPFC | 10 | 20 Hz |
| Srovnalova 2011 | 10 | 66.0 | 5.4 | Left and right inferior frontal gyri | 1 | 25 Hz |
| Srovnalova 2012 | 10 | 66.0 | 5.4 | Left DLPFC | 4 | 25 Hz |
| Benninger 2009 | 9 | 62.6 | | Left M1 | 1 | 50 Hz |

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;
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. A Q test was used to analyze the heterogeneity among the studies. When there were statistics among the studies ($I^2 \leq 50 \%)$, the fixed effect model was used for meta-analysis. On the contrary, meta-analysis was conducted with randomized effects model. In addition, 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. 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 as well as excluding duplicate documents, 14 documents were finally left that met the criteria. The detailed article screening process is 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, working memory, attention, and language function). All articles contained the data immediately after the treatment, and only three articles had long-term follow-up data.

Characteristics of the patients with PD
A total of 249 subjects were included in the 14 studies, 70 subjects of which also suffered from depression, and 163 subjects of which included in this study. 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. A few studies have reported this in detail but nothing existed on clinical heterogeneity on the patient’s motor symptoms was included in the studies. Most patients had cognitive deficit, including six patients who suffered from dementia. The ages of all patients were over 60 years old, and about 10 of them were over 70 years old. 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 which indicated most patients had a high risk of cognitive impairment. Most patients had stable medications for a period of time before treatment and during treatment, but the studies lacked detailed information on the specific medications.

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. 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, and the rest did not report the number. No adverse reactions were reported in the remaining six studies. Mild headache was the main side effect. Individual patients had symptoms such as fear, headache, tinnitus, dizziness, hearing loss, fainting, nausea, but no serious side effects (Table 2).

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

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 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. shows that due to inconsistency of the overall cognitive scale may lead to deviations in results, we conducted detailed analyses through unified scale further.
| 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*           |
| Benning2009  | 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*           |

**Different scale subgroup results**

The cognitive scales were divided into Mattis Dementia Rating Scale (DRS) group, Mini-Mental State Examination (MMSE) group, and Montreal Cognitive Assessment (MoCA). 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. shows 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 functions, working memory, attention functions, and language functions. Among them, 11 studies related to executive function included 166 patients; eight studies related to working 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) shows the left and right are basically symmetrical. This indicates that there was no or slight publication bias. The result is 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 deficit of PD patients. On the whole, the results of publish works showed the 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, the meta-analysis [18] showed that rTMS treatment had no significant effects on cognitive recovery in PD patients. The main reason was that only three articles in the study contained a limited number of subjects. In our study, 14 studies including more subjects and showed that rTMS treatment played a positive role in the improvement of cognitive deficit which was similar to previous review of Anderkova et al. [15] in 2017. Moreover, the review of Dinkelbach et al.[16]confirmed rTMS over prefrontal areas can lead to an enhancement of cognitive functions that are predominantly impaired in PD. In fact, the efficacy of rTMS on cognition was reported in other mental illness meta-analysis, For example, in both dementia [21] and schizophrenia [9], studies have shown rTMS was a feasible therapeutic method. For the diagnosis and study of PD cognitive function, clinical neuropsychology and cognitive neuroscience offer a variety of testing tools such as the Montreal cognitive scale, the PD cognitive rating scale, the Mattia DRS, and the MMSE. 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 the MoCA scale, small sample size may result in deviation of results, so our study focused on MMSE scale and DRS scale. 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 proportion of concept bias is larger (39/144). It can
be seen from the above that both scales have a tendency toward different cognitive fields. 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. These may be part of the cause of the deviation of the results. Indeed, DRS is generally more sensitive and specific for general cognitive impairment assessment than MMSE. Even Monsch et al. [22] found the DRS scale had a good discriminative effect on memory, onset, and persistence which was beneficial for rapid screening for dementia patients, but our study included PD patients with cognitive impairment who had clinically heterogeneous motor symptoms, and some even had moderate and major depressive symptoms. The crossover of these complex symptoms could be a factor in this outcome. Of course, we cannot deny that the low sensitivity of MMSE scale leads to the deviation of the results. Up to now, non-specific cognitive scale is mostly used in the evaluation of PD cognitive disorder, with low sensitivity and heterogeneity. Ideal PD cognitive function evaluation tools should include 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 from different cognitive domains showed executive dysfunction of PD patients obtained significant improvement from rTMS therapy; especially when the frequency of stimulus was high frequency. The stimulation site was located in the DLPFC, and the session of stimulation was not single. Similar results have been reported in previous studies. For example, Mogg’s study found that a 10 days courses of high rTMS posited on DLPFC had some improvement on the executive function of schizophrenia. In addition, Moser et al. [23] 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 functions 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 [24]. 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 [25]. 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 [26].

One previous study [27] 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 [28, 29].

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 have different 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. [30] 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 [31, 32]. 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 working 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 [33, 34]. 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 [6]. 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. For example, during the progression of dementia, there is a large amount of neurofibrillary tangles and amyloid deposits in the brain which are accompanied by a decline in axonal transport function and loss of neurons [35]. This may affect the rTMS treatment outcome. Therefore, although the structural anatomy of working 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[36, 37]. Some imaging studies [38] 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,[39, 40] and the damage of the parietal structure also leads to visual neglect. [41] Hilgetag et al. [42] 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 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 impairment, but there is no uniform standard in the world. The poor directivity and specificity of some scales may lead to some deviations in the results. Finally, a large number of articles have no data after follow-up, so that we could not analyze the long-term effects of rTMS treatment. In later studies, we hope to have some large sample of experiments involving long-term follow-up effect after treatment 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 dysfunction 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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Figures
Figure 1

Study screening flow char.
### Figure 2

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

Figure 3

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

2.3.2. Executive Function

Figure 4

Stimulation frequency subgroup results after rTMS on executive function.
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.
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.

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