

# Recent Research Progress on the Use of Transcranial Magnetic Stimulation in the Treatment of Vascular Cognitive Impairment

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**Abstract:** Vascular Cognitive Impairment (VCI) is a condition where problems with brain blood vessels lead to a decline in cognitive abilities, commonly affecting the elderly and placing a significant burden on both patients and their families. Compared to medication and surgery, Transcranial Magnetic Stimulation (TMS) is a non-invasive treatment option with fewer risks and side effects, making it particularly suitable for elderly patients. TMS not only assesses the excitability and plasticity of the cerebral cortex, but its effectiveness in treating Vascular Cognitive Impairment (VCI) and its subtypes has also been validated in numerous clinical trials worldwide. However, there is still a lack of review on the physiological mechanisms of TMS treatment for VCI and its specific clinical application parameters. Therefore, this article initially provided a brief overview of the risk factors, pathological mechanisms, and classification of VCI. Next, the article explained the potential physiological mechanisms of TMS in treating VCI, particularly its role in promoting synaptic plasticity, regulating neurotransmitter balance, and improving the function of the default mode network. Additionally, The article also summarizes the application of rTMS in treating VCI and its subtypes, VCI-related sleep disorders, and the use of TMS in follow-up studies of VCI patients, providing empirical evidence for the clinical application of TMS and rTMS technologies.

**Keywords:** transcranial magnetic stimulation, mild cognitive impairment, post-stroke dementia, VCI-related sleep disorders, following up VCI patients, physiological mechanism

## Introduction

Vascular Cognitive Impairment (VCI) is a broad term used to describe a range of disease states in which cognitive decline is caused or exacerbated by cerebrovascular problems. Patients with VCI may present with a complex array of clinical symptoms, including memory loss, scattered attention, impaired executive functioning, language impairment, and spatial cognitive decline.<sup>1</sup> In addition to these symptoms, all of which can directly affect cognition, individuals with VCI may also suffer from a range of behavioral and emotional challenges, such as apathy, irritability, depression, or psychomotor slowing, which are additional symptoms that also pose significant challenges to patients and their carers.<sup>2,3</sup> The prevalence of VCI is substantial in the elderly population. One cross-sectional study conducted by Capital Medical University in 2020 revealed that the prevalence of vascular dementia in the elderly population is approximately 1.6%, making it the second most common subtype of dementia after Alzheimer's disease.<sup>4,5</sup> Although VCI is not associated with mortality, this disease dramatically affects people's quality of life, imposing a significant



financial burden on the social healthcare system. Currently, no drugs are available for the specific treatment of VCI in the clinic, meaning that other non-invasive, non-pharmacological treatment options must be explored.

Transcranial Magnetic Stimulation (TMS) has increasingly gained attention in the clinical field as a safe and non-invasive method of neural modulation, which has shown significant therapeutic effects in the treatment of depression, anxiety, and other neurological disorders.<sup>6,7</sup> This technology is not only widely used in clinical therapy but also in scientific research and clinical diagnosis. It enables real-time assessment of motor areas, corticospinal tracts, and neural pathways in conditions including cognitive impairment and dementia. Consequently, this capability is frequently utilized to aid in the diagnosis and differentiation of various types of dementia.<sup>7</sup> As such, it is also commonly used to assist in diagnosing various types of dementia.<sup>8</sup> Additionally, researchers such as Mariagiovanna Cantone have used TMS to reveal the gender differences in the population with VCI for the first time, finding that men with mild VCI exhibit poorer cognitive abilities and functional status compared with their female counterparts.<sup>9</sup> Common application modes of TMS include single pulse TMS (sTMS), paired pulse TMS (pTMS), and repetitive TMS (rTMS).<sup>10</sup> rTMS is a specific mode of TMS technology characterized by the use of repeated magnetic pulses to influence neural activity in brain regions. Compared to other application modes of TMS, rTMS is more commonly used in clinical treatment, and is particularly effective in treating cognitive impairments in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD).<sup>11</sup>

TMS is a technique based on the principles of electromagnetic induction and transformation. It utilizes transient electrical currents in a stimulation coil to generate a magnetic field, which can penetrate the skull and induce currents in specific brain regions, thereby activating neuronal action potentials. This method effectively modulates neural physiological activity, influencing the associated behavioral responses.<sup>12</sup> The main characteristics of TMS include its ability to deeply stimulate the cerebral cortex and precisely modulate specific brain areas, offering highly adjustable therapeutic effects. The therapeutic outcomes of TMS are also known to be influenced by the stimulation frequency: low-frequency stimulation (less than 1 Hz) typically inhibits cortical activity, while high-frequency stimulation (greater than 5 Hz) enhances cortical excitability. Additionally, the effects induced by TMS are also affected by the intensity and duration of the stimulation, as well as the specific brain areas targeted. Therefore, varying stimulation parameters can lead to different neurophysiological responses, thus affecting the therapeutic outcomes of TMS.

## Methods

A literature search was carried out to find all the relevant studies on TMS and rTMS in VCI. A search was conducted to identify studies published from the establishment of the database to December 25, 2023, using keywords such as “repetitive transcranial magnetic stimulation”, “transcranial magnetic stimulation”, “vascular cognitive impairment”, “vascular dementia”, “mild cognitive impairment”, and “clinical study”.

Two authors independently screened the titles and abstracts of the retrieved publications to reach a consensus. Duplicates, retracted publications, studies lacking statistical analysis of clinical data, non-English papers, and any other articles that did not fit the scope of this review (such as migraine, anxiety disorders, epilepsy, obsessive-compulsive disorder, movement disorders and neurological surgeries) were excluded. The references listed in the articles were also reviewed to search for additional data.

## Vascular Cognitive Dysfunction

### Risk Factors and Pathological Mechanisms of VCI

Given that vascular factors are the primary cause of VCI, it is particularly important to control these risk factors and maintain vascular health. Vascular risk factors primarily include high blood pressure, high cholesterol, depression, and other lifestyle-related factors. High blood pressure is one of the most significant risk factors for VCI, because it can cause long-term damage to cerebral blood vessels and changes in vascular structure, which in turn affect brain hemodynamics and metabolism, leading to cognitive dysfunction. Additionally, high blood pressure can also trigger typical acute cerebrovascular complications, such as ischemic or hemorrhagic strokes, which can directly impair cognitive functions. In cases of hypertensive crises, brain magnetic resonance imaging often reveals areas of high signal intensity in the white matter, indicating structural and functional damage to the white matter, subsequently affecting the brain's executive functions and attention.<sup>13</sup> In recent years, depression has also

been considered as one of the potential risk factors for VCI. Studies indicate a clear association between depression and impaired cognitive function, especially among the elderly.<sup>14</sup> Depression is also one of the most common neuropsychiatric precursors of dementia in the elderly.<sup>15</sup> Research by Jianjun Wang and others has suggested that depressive symptoms may be a reversible factor in the decline of cognitive abilities in the elderly, while controlling depression could help slow the irreversible decline in cognitive function.<sup>16</sup> Although no genetic risk factors directly associated with VCI have yet been identified, certain hereditary diseases that predispose individuals to recurrent strokes may increase the risk of developing VCI.<sup>17</sup>

The neuropathology of VCI shows significant complexity and heterogeneity, with pathological changes and cognitive impairment being closely linked. VCI often originates from endothelial dysfunction and damage caused by vascular risk factors, and may further lead to a series of vascular-related lesions, including cerebral infarction, white matter disease, cerebral hemorrhage, chronic cerebral hypoperfusion, microvascular disease, endothelial dysfunction, blood-brain barrier damage, and neuroinflammation. Notably, the pathological processes underlying VCI often involve the interaction of these various vascular lesions, and in many cases, the pathology of VCI is intertwined with neurodegenerative changes.

### Typology of VCI

According to the Guidelines for the Diagnosis and Management of Vascular Cognitive Impairment published in 2011, VCI can be classified into five subtypes based on the etiology and pathological mechanisms, which are as follows: risk factor-related VCI, ischemic VCI, hemorrhagic VCI, other types of cerebrovascular disease-associated VCI, and VCI in which cerebrovascular disease coexists with AD (Figure 1). In 2017, the International Cognitive Vascular Impairment Classification Consensus Studies (VICCS-1 and VICCS-2) collected and reviewed the conceptual literature on VCI.<sup>18</sup> This study classified the diagnostic criteria into two categories based on the severity of VCI: MCI and vascular dementia (VaD). The VICCS-1 further detailed four subtypes of severe VCI based on the patient’s history of stroke, clinicopathological features, and imaging manifestations: post-stroke dementia, subcortical ischemic vascular dementia, multiple infarct dementia, and mixed dementia (Figure 1).<sup>19</sup>

## Physiological Mechanisms Underlying the Utility of TMS in the Treatment of VCI

### TMS Modulates Synaptic Plasticity to Improve VCI

Synaptic plasticity refers to the ability to form new connections between nerve cells in the brain, or to make persistent adjustments to the strength of existing connections. This process is a critical mechanism in learning and memory formation. In experimental studies, Long-Term Potentiation (LTP) and Long-Term Depression (LTD) are often used to

Correlation of risk factors VCI	Ischemic VCI	Hemorrhagic VCI	Other cerebrovascular VCI diseases	Cerebrovascular disease combined with AD
According to the etiology and mechanism of vascular brain injury classification				
VCI				
According to the severity of cognitive impairment classification				
MCI	Major(VaD/VCD)			
The patient's cognitive decline is not sufficient to diagnose dementia or to interfere with the instrumental activities of daily living	Post-stroke dementia	Subcortical ischemic	Multi-infarct dementia	Mixed dementia
	Immediate and/or delayed cognitive decline within 6 months after stroke in patients who have not recovered.	Vascular dementia caused mainly by small vessel lesions	Multiple large infarcts involved in vascular dementia	Cognitive impairment due to other comorbidities, including VCI-AD, VCI-DLB, etc.

Figure 1 Typology of vascular cognitive impairment.

describe the increase and weakening of the strength of synaptic connections, respectively.<sup>20</sup> TMS can induce plastic changes in brain synapses by modulating the firing activity of neurons, including strengthening or weakening synaptic connections and forming new synapses.<sup>21</sup> Synaptic plasticity exhibits different patterns depending on the stimulation parameters; for example, high-frequency TMS (especially intermittent electrical stimulation mode, ITBS) tends to induce LTP, while low-frequency and continuous electrical stimulation (CTBS) modes predominantly elicit LTD. TMS-induced LTP and long-term inhibitory effects have been demonstrated in *in vitro* neuronal studies in non-human subjects. Lenz et al further demonstrated that TMS induces plastic changes in excitatory and inhibitory synapses on internal olfactory hippocampal slices in mice.<sup>22,23</sup> In addition, the ability of TMS to improve cognitive function by modulating synaptic plasticity has also been demonstrated in animal models. In 2014, Ma Jun et al found that low-frequency TMS was able to enhance cognitive function by improving synaptic plasticity in the hippocampus in a senescent mouse model.<sup>24</sup> Subsequently, in 2015, Zhang Y et al observed in a rat model of vascular dementia that TMS enhanced cognitive function via action on the vascular endothelial growth factor (VEGF) and Brain-Derived Neurotrophic Factor-N-Methyl-D-Aspartate Receptor (BDNF-NMDAR) pathways, enhancing spatial learning ability and synaptic plasticity.<sup>25</sup> Conversely, TMS was also able to increase the level of BDNF in the hippocampus, which, as a critical regulator of synaptic plasticity, plays a vital role in neuronal growth and survival, as well as the enhancement of brain function.<sup>26</sup>

TMS activates the brain regions associated with specific cognitive tasks through customized stimulation protocols, promoting synaptic plasticity in these regions and enabling them to participate more effectively in mental activities. This strategy significantly supports cognitive function and offers a practical pathway for treating cognitive impairment.

## TMS Modulates Neurotransmitter Release to Improve VCI

Neurotransmitters play a crucial role as messengers in the brain, transmitting signals through synapses between neurons. Due to this role, they have a profound effect on cognitive functions such as learning, memory, attention, and decision-making. Different neurotransmitters regulate different mental and emotional processes in the brain. TMS can regulate neurotransmitters by inducing electrical activity in neuronal cell membranes, which in turn changes the activity of ion channels.

Glutamatergic and gamma-aminobutyric acid (GABA) neurotransmission both play critical roles in modulating the excitatory or inhibitory effects of TMS on the brain. For example, Huang et al found that glutamate receptor antagonists, such as memantine, blocked the enhancement of activity in the human motor cortex by inducing intermittent theta-burst stimulation (iTBS), as well as the inhibitory effects of continuous theta-burst stimulation (cTBS).<sup>27</sup> Many recent studies have pointed out that the improvement of cognition by TMS is closely related to glutamatergic and GABAergic neurotransmission. Observations in a mouse model of AD have suggested that TMS may promote cognitive improvement by increasing glutamate clearance.<sup>28</sup> In 2023, an article in the journal *Neurochemistry International* reported that TMS enhanced memory by increasing glutamate levels and theta wave oscillations in the hippocampus of healthy rats, while also reducing GABA levels.<sup>29</sup>

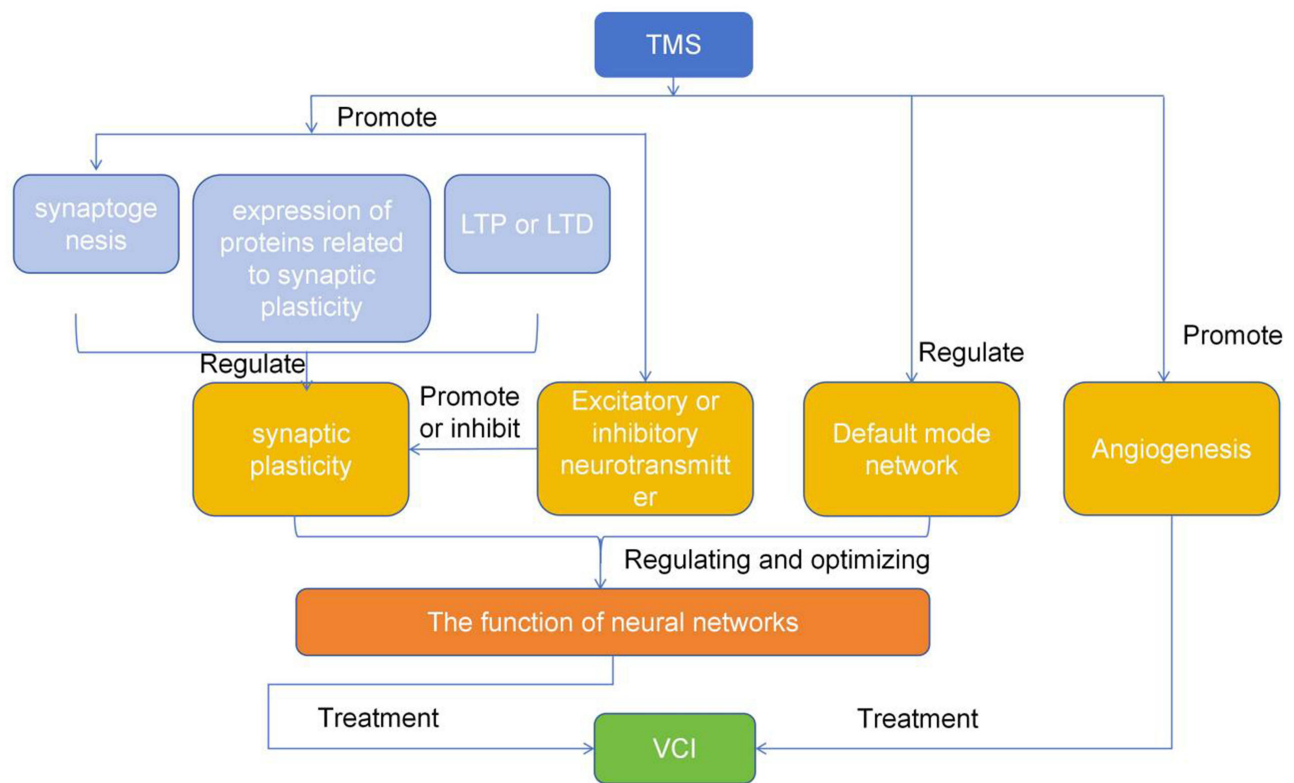
The cholinergic neurotransmitter system is strongly associated with functions such as learning, memory, attention, and cognitive flexibility. Based on the results of clinical trials reported so far, we can say that the activity of the central cholinergic system is significantly reduced in patients with AD and MCI.<sup>30,31</sup> Therefore, many strategies for treating dementia have focused on boosting cholinergic transmission activity. Low-frequency TMS was found to improve deficits in learning and memory, increase acetylcholinesterase and choline acetyltransferase activities, and increase the density of cholinergic neurons and the number of BDNF immunoreactive cells in a rat model of vascular dementia.<sup>32</sup> However, no significant impairment of cholinergic system activity has been observed in past studies of patients with vascular cognitive impairment-no dementia (VCI-ND).<sup>33</sup>

In addition, the role of TMS in promoting cognitive function may also be related to the modulation of dopamine neurotransmission. In one double-blind, randomized controlled trial involving 45 adult participants conducted by Wang, Ying et al, dopamine neurotransmission was found to play an essential role in the regulation of cortical excitability by TMS, with the most pronounced effects on dopamine receptor D4 (DRD4).<sup>34</sup> Considering the close association of DRD4 with cognition, memory, and LTP functions, improving cognitive functions by TMS may be closely related to the modulation of dopamine levels.<sup>35</sup>

## TMS Modulates the Default Mode Network to Improve VCI

The default mode network (DMN) is a neural network consisting of the medial prefrontal cortex (MPFC), posterior cingulate cortex, precuneus, hippocampus, inferotemporal cortex, and inferior parietal lobule.<sup>36</sup> TMS is active when the brain is at rest.<sup>37</sup> The DMN is activated when the brain relaxes, and this phenomenon is closely associated with self-reflection, memory, and mental roaming. Research has shown that TMS is not limited to areas that are directly stimulated, indeed, it also affects other brain regions through neural network interactions, thereby inducing persistent changes in inter-brain connectivity, which forms the basis of the cognitive improvements facilitated by TMS. In both AD amnesic mild cognitive impairment (aMCI), the DMN presents abnormal activity.<sup>38</sup> Studies have shown that the improvements in cognitive function observed in aMCI patients treated with TMS is associated with weakening DMN internal connections.<sup>39</sup> In addition, TMS has been associated with improved cognitive deficits in patients with post-stroke cognitive impairment (PSCI), which has been linked to increased resting-state brain activity in the left MPFC, as well as enhanced functional connectivity in the right MPFC and the right ventral anterior cingulate cortex.<sup>40</sup> Tang et al previously demonstrated that cognitive training improves subcortical VCI or dementia patients' overall cognitive function, and significantly enhances connectivity between the left dorsolateral prefrontal cortex (DLPFC) and MPFC, emphasizing the importance of brain network functional connectivity in mental recovery.<sup>41</sup>

Clinical studies have shown that the application of TMS stimulation to a patient's prefrontal cortex (PFC) triggers the release of endogenous dopamine in the ipsilateral caudate nucleus. This process significantly promotes synaptic functional plasticity, positively affecting cognitive function.<sup>42</sup> Additionally, rTMS affects the dynamic functional connectivity of the DMN by improving the synaptic plasticity of neurons within this network.<sup>43</sup> These findings suggest that the effects of rTMS in promoting cognitive function occur as a result of multiple mechanisms that are interconnected and interact with each other.(Figure 2)



**Figure 2** Physiological mechanisms underlying the utility of TMS in the treatment of VCI.

## TMS Promotes Angiogenesis to Improve VCI

At present, the exact mechanisms underlying the vascular effects of TMS are still only incompletely understood. However, based on fundamental studies in animal models of ischemic stroke, researchers have found that TMS promotes the release of angiogenesis-related factors, including transforming growth factor  $\beta$  (TGF $\beta$ ) and VEGF, from A2 astrocytes, thereby promoting neovascularization. Similarly, in stroke-model rats, theta-burst TMS has been found to promote neovascularization and protect the vasculature.<sup>44</sup> At the clinical level, Koch et al's experiments have also demonstrated the positive effects of TMS on the restoration of function in patients with hemiplegia who have suffered consecutive ischemic chronic stroke.<sup>45</sup> These findings suggest that TMS may improve vascular function and promote neurological recovery through multiple pathways, providing new perspectives for the future treatment of vascular-related diseases.

## Clinical Use of rTMS in VCI and Its Subtypes

In recent years, rTMS has been widely studied and applied internationally to treat neurological disorders. Although the number of related studies continues to increase, more discussion regarding its application in the treatment of VCI is needed, particularly in clinical trials. Therefore, this study aimed to summarize and analyze the information available on the PubMed website regarding the application of rTMS in the treatment of VCI and its subtypes, particularly in regards to specific details on therapeutic parameters and stimulation sites, to provide valuable data to support future research in this area. Through the data analysis summarized in [Table 1](#), we found that rTMS is usually applied in a high-frequency mode when treating patients with MCI and PSCI. The stimulation area is mainly focused on the left hemisphere of the brain or the bilateral hemispheres, particularly in the dopaminergic prefrontal cortex (DLPFC) or the PFC regions. In addition, an effective treatment program usually requires a minimum of 20 sessions and a stimulation intensity of no less than 80% of the resting motor threshold (rMT).<sup>46,47</sup>

As research into repetitive rTMS for the treatment of VCI and its subtypes deepens, researchers are no longer limiting the site of stimulation to the DLPFC. For example, it has been shown that by applying high-frequency rTMS applied to the right inferior frontal gyrus (IFG) of the brain can significantly enhance attention and psychomotor speed in patients with MCI or mild dementia due to AD.<sup>48</sup> In 2023, the Department of Rehabilitation at the Shanghai University of Medical and Health Sciences initiated a single center, single-blind, randomized controlled trial, enrolling 57 patients with PSCI, with the aim of comparing the effects of dual-target versus single-target rTMS treatment with simultaneous stimulation of the left DLPFC and the ipsilateral M1 region on cognitive function in patients with PSCI.<sup>49</sup> In addition, high-frequency rTMS stimulation of the left DLPFC significantly reduced apathy symptoms in patients with MCI.<sup>50</sup> Although most current clinical trials favor high-frequency rTMS for treatment, some researchers have also found that low-frequency rTMS stimulation of the right DLPFC also improves memory.<sup>39</sup> In contrast, stimulation of the inferior frontal gyrus enhances executive function in patients.<sup>51</sup> However, due to the small sample size of low-frequency rTMS studies, the credibility of these results has yet to be further validated.

## The Role of rTMS in Treating VCI-Related Sleep Disorders

Patients with VCI often experience sleep disorders, which in turn are a significant risk factor for vascular dementia and may accelerate the progression of VCI. There is a close bidirectional relationship between the two.<sup>52</sup> The safety and feasibility of using rTMS to treat insomnia disorders (ID), obstructive sleep apnea syndrome (OSAS), restless legs syndrome (RLS), and cognitive impairments associated with sleep deprivation (SD) have been established.<sup>53</sup> However, the specific application of rTMS needs to be individually adjusted based on different types of sleep disorders. High-frequency(10Hz) rTMS stimulation of the left dorsolateral prefrontal cortex (LDLPFC) can alleviate cognitive impairments caused by sleep deprivation (SD).<sup>54</sup> Meanwhile, low-frequency (1Hz) rTMS stimulation of the LDLPFC significantly improves conflict control abilities and sleep quality in patients with insomnia.<sup>55</sup> For patients with RLS, administering 15Hz rTMS to the left primary motor cortex (M1) can improve cognitive functions.<sup>55</sup>

Sleep is not a static phase or merely the opposite of wakefulness; it is a dynamic process involving functional and structural changes, including alterations in cerebral blood flow, neurotransmitter release, synaptic strength, immune

**Table 1** Summary of Previously Published Clinical Articles Related to rTMS in the Treatment of Vascular Cognitive Impairment

VCI Subtypes	Study, Year	Number of Cases(N)	Stimulation Parameters(Intensity, Frequency, Number of Pluses, Stimulation Time, Interval)	Stimulus Area	Course of Treatment	Main Findings
PSCI	Cha, Byoungwoo et al <sup>47</sup>	10	100%RMT; 20 Hz; 2000 pulses; 5s; 55s.	DLPFC	Once a day; 5 days a week; Two consecutive weeks.	rTMS significantly improves cognitive function
	Xu, Bingshan et al 2023 <sup>45</sup>	57	80%RMT; 10 Hz; 2000 pulses; 5s; 25s.	L-DLPFC, ipsilesional M1	Once a day; 5 days a week; four consecutive weeks.	Comparison of rTMS dual-target and single-target efficacy in the treatment of PSCI
	Yin, Mingyu et al 2020 <sup>35</sup>	34	80% RMT; 10 Hz; 2500 pulses; 5s; 25s.	L-DLPFC	Once a day; 5 days a week; four consecutive weeks.	Improved cognition with rTMS is associated with the modulation of resting-state brain activity and functional connectivity
	Chu, Minmin et al 2022 <sup>44</sup>	60	70%RMT Inter-cluster stimulation 50H, intra-cluster count 3; Inter-cluster frequency 5 HZ, number of clusters 20; 600 pulses; 2s; 8s.	DLPFC	Once a day; 5 days a week; Six consecutive weeks.	Cognitive improvement with iTBS is based on activation at the stimulation site and some distant regions
Early AD	Eliasova, Ilona et al <sup>43</sup>	10	90%RMT; 10 Hz; 2250 pulses; 4.9s; 25s.	R-IFG; R-STG; Vertice.	Once a day; One day at a time; Two times in total.	High-frequency rTMS of the right IFG significantly improves cognitive function in AD patients

(Continued)

Table I (Continued).

VCI Subtypes	Study, Year	Number of Cases(N)	Stimulation Parameters(Intensity, Frequency, Number of Pluses, Stimulation Time, Interval)	Stimulus Area	Course of Treatment	Main Findings
MCI	Padala, Prasad R et al 2018 <sup>47</sup>	9	120%RMT; 10 Hz; 3000 pulses; 4s; 26s.	DLPFC	Once a day; 5 days a week; two weeks of treatment 4 weeks off in between; Total 8 weeks of treatment.	rTMS is effective in improving apathy in MCI subjects
	Cui, Hailun et al 2019 <sup>34</sup>	21	90%RMT 10Hz; 1500 pulses; 5s; 245s,	R-DLPFC	Once a day; 5 days a week; Two consecutive weeks.	Improved clinical cognitive improvement in MCI patients with rTMS is associated with modulation of connectivity within the DMN
	Wang, Tao et al 2023 <sup>46</sup>	40	90%RMT; 10 Hz; 1500 pulses; 5s; 25s.	L-DLPFC	Total of 10 treatments	L-DLPFC's high-frequency rTMS can improve memory impairment by modulating neuronal activity and brain networks.

**Notes:** Table I: Resting Motor Threshold (RMT) is the lowest stimulus intensity that can be evoked at least 50% of the time in a limited number of trials (typically 10 trials).

**Abbreviations:** STG, Superior Temporal Gyrus; DLPFC, Dorsolateral Prefrontal Cortex; M1, First Motor Area.



responses, and metabolic states. Therefore, rTMS may treat sleep disorders associated with VCI by modulating cortical excitability, improving circadian rhythms, enhancing connectivity between brain regions, and promoting neuroplasticity. Interestingly, while clear changes in electrophysiological markers related to cortical plasticity have been observed in patients with OSAS and RLS,<sup>56</sup> these changes are not seen in patients with sleep fragmentation (SF).<sup>57</sup> Therefore, the specific mechanisms by which rTMS treats cognitive impairments related to VCI still require further exploration.

## The Application of TMS in Follow-Up Patients with VCI

Unlike degenerative dementias, Mild vascular cognitive impairment can be prevented and potentially reversed before it progresses to full-blown dementia. Therefore, it's crucial to monitor and follow up with VCI patients regularly. TMS not only demonstrates significant effectiveness in treating neurological disorders, but it also serves as a diagnostic tool. In both clinical settings and scientific research, TMS is used to assess cortical plasticity and central neurotransmitter pathways by monitoring changes in specific TMS parameters.<sup>58</sup> For instance, in patients with AD and VaD, TMS diagnostics have revealed a reduction in the resting motor threshold (rMT) of the cortical areas, indicating excessive cortical excitability and impaired plasticity.<sup>59,60</sup> This increased excitability in the motor cortex is considered a compensatory reaction to the loss of neuronal plasticity.<sup>61</sup> Research has confirmed that a persistent decrease in rMT is significantly correlated with disease progression over a year.<sup>62,63</sup> Additionally, in a two-year follow-up study of patients with non-demented vascular cognitive impairment (VCI-ND), a reduction in rMT was also observed, further underscoring the important role of TMS in tracking and understanding these conditions. Paired-pulse TMS is used to evaluate intracortical facilitation (ICF) in the brain's cortex. Changes in ICF can reveal disruptions in excitatory neurotransmitter cortical circuits, such as glutamatergic and dopaminergic pathways. In a study, Rita et al observed an increase in intracortical facilitation (ICF) among elderly patients without dementia and those with subcortical ischemic vascular disease.<sup>64</sup> Additionally, short-latency afferent inhibition (SAI), a TMS measure for assessing central cholinergic cortical pathway function, is markedly abnormal in primary cholinergic forms of dementia such as AD and amnesic Mild Cognitive Impairment (aMCI). However, in patients with non-demented vascular cognitive impairment (VCI-ND), SAI showed no significant changes, suggesting that their cholinergic systems may remain relatively stable. However, the lack of significant changes in short-latency afferent inhibition (SAI) among patients with non-demented vascular cognitive impairment (VCI-ND) suggests that the central cholinergic pathways may not be involved in the pathology of VCI-ND.<sup>33</sup>

## Current Limitations and Future Applications

Currently, research into the use of rTMS for the treatment of diseases such as vascular dementia faces several challenges, most notable that the sample sizes of clinical trials are too small, which limits the wide acceptance and credibility of the findings. As seen in Table 1, although there are a relatively large number of clinical trials investigating the use of rTMS for MCI and PSCI, the number of patients enrolled has rarely exceeded 100. Clinical trials conducted are even scarcer for other subtypes of VCI. In addition, one challenge such studies face is the difficulty of recruiting sufficient numbers of elderly healthy controls, which results in a lack of neuroimaging evidence of cerebrovascular disease associated with controls. As a result, it is challenging to construct a systematic and prescriptive set of treatment guidelines from current research in this area.

The most well-known application of TMS is in the treatment of depression, and it is also widely used to treat obsessive-compulsive disorder (OCD), anxiety, chronic pain, schizophrenia, and in rehabilitation training after strokes. As research progresses, the potential of TMS in treating neurodegenerative diseases, such as AD, Parkinson's disease, and other cognitive degenerative disorders, is becoming increasingly evident. In diagnosis and differential diagnosis, TMS can assess the excitability and plasticity of the cerebral cortex under different disease conditions, and can also detect the integrity and functional state of neural circuits by combining it with electroencephalography (EEG).<sup>65</sup> 15Dual-pulse TMS is used to assess the functional connectivity of brain networks<sup>16</sup>, and the electrophysiological indicators of TMS can also serve as early biomarkers for the progression of mild vascular cognitive impairment (VCI) to dementia.<sup>66</sup>

## Conclusion

As an innovative, non-invasive neuromodulation tool, rTMS has the potential to open new therapeutic avenues in the treatment of VCI. Current research has shown that rTMS has significant therapeutic potential for cognitive dysfunction, behavioral and mood disorders, and even neurodegenerative diseases, functioning by modulating synaptic plasticity, neurotransmitters, and DMN, and promoting angiogenesis in the brain. Furthermore, rTMS can also be applied in the early diagnosis and assessment of diseases,<sup>52</sup> playing an essential role in the differential diagnosis of some diseases. The recent discoveries made in studies using rTMS in animal models are exciting; however, the clinical significance of rTMS still needs to be verified due to the small number of clinical samples. It will be necessary to combine clinical examination, psycho-cognitive assessment, and neuroimaging to systematically evaluate the diagnosis and treatment effects of rTMS in patients with VCI, which in turn could help the early diagnostic process of VCI, enhance the treatment of VCI, and help physicians predict the prognosis of VCI.

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The authors report no conflicts of interest in this work.

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