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REVIEW

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A Review on Combined Strategy of Non-invasive Brain Stimulation and Robotic Therapy

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Abstract

Stroke is a major cause of death and disability among adults in China, and an efficient rehabilitation strategy has been an urgent demand for post-stroke rehabilitation. The non-invasive brain stimulation (NBS) can modulate the excitability of the cerebral cortex and provide after-effects apart from immediate effects to regain extremity motor functions, whereas robotic therapy provides high-intensity and long-duration repetitive movements to stimulate the cerebral cortex backward. The combined strategy of the two techniques is widely regarded as a promising application for stroke patients with dyskinesia. Transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (TES) are important methods of NBS. Their recovery principles, stimulation parameters, and clinical applications have been summarized. The combined treatments of rTMS/tDCS and robotic therapy are analyzed and discussed to overcome the application barriers of the two techniques. The future development trend and the key technical problems are expounded for the clinical applications.

Keywords Stroke, Non-invasive brain stimulation, Robotic therapy, Combined strategy

1 Introduction

Stroke is a significant factor contributing to death and functional impairment among adults in China presented in the latest report on stroke prevention and rehabilitation [1]. An efficient rehabilitation strategy has been an urgent demand for post-stroke rehabilitation. Physiotherapy and occupational therapy have been recommended as conventional methods for dyskinesia of upper or lower limbs in the Chinese Stroke Rehabilitation Guidelines (2011) [2]. Mirror therapy, motor imagery, virtual reality, brain-computer interface (BCI), and non-invasive brain stimulation (NBS) are proposed with the continuous development of rehabilitation techniques and interdisciplinarity. Both BCI and NBS have the potential to facilitate neurorehabilitation and provide assistive technology solutions for individuals with motor impairments. NBS mainly focuses on modulating the excitability of neurons in targeted brain areas to benefit neurological rehabilitation, while BCI mainly focuses on establishing direct communication pathways between the brain and external devices or computer systems.

Notably, NBS can modulate the excitability of the cerebral cortex and provide after-effects apart from immediate effects. The combination of NBS and robotic therapy offers several advantages over using Stimuli such as electrical stimulation, visual stimulation. Some of the key advantages include targeted stimulation, personalized treatment, and long-lasting effects. NBS can target specific brain regions associated with motor function or recovery, enhancing the effectiveness of robotic therapy by modulating neural activity in these areas. Based on the specific needs and response to stimulation of individual

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patients, NBS can be tailored to make the therapy more personalized and potentially more effective. The combination of NBS and robotic therapy may lead to longer-lasting improvements in motor function and recovery by inducing changes in neural connectivity and promoting neuroplasticity. Robotic rehabilitation techniques have also incorporated the advantage of engaging patients' subjective involvement seen in visual stimulation. Currently, various rehabilitation robots have been developed with accompanying rehabilitation games. These robots utilize sensors and host computer interfaces to assist patients in relearning and improving motor function, balance, and spatial perception. Previous studies have shown that it is difficult for a single treatment to achieve the expected results. The combined treatment of NBS and robotic therapy is applied in clinics generally to complete neuromuscular training. In addition, the evaluation indexes of the motor nervous system and limb function can be obtained to predict the rehabilitation effect in advance compared with functional evaluation scales (MBI, UFMA, etc.). The rehabilitation strategy also can be optimized according to the evaluation indexes.

The transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (TES) are the major methods of NBS. Their recovery principles, stimulation parameters, and clinical applications have been summarized. The combined treatments of rTMS/tDCS and robotic therapy are analyzed and discussed to overcome the application barriers of the two techniques.

2 Methods

2.1 Search Strategy

The systematic review was conducted by performing a literature search with Web of Science, PubMed, Scopus, IEEE Xplore, and CNKI, and the search was limited to English and Chinese language articles (i.e., journal articles and conference proceedings) published up to July 2023. The electronic search keywords were 'stroke OR spinal cord injury' AND 'robotic therapy OR robot-assisted OR exoskeleton' AND 'non-invasive brain stimulation OR transcranial magnetic stimulation OR transcranial direct current stimulation'. Appropriate syntax using Boolean operators and wildcard symbols was used for each database to include a wider range of articles that might have used alternate spellings or synonyms.

2.2 Inclusion Criteria

Studies were eligible for inclusion if the following criteria were met:

- Studies participants should be adults (age > 18 years);
- Studies should give outcomes, including the effects of NBS;
- Studies should recruit more than five participants;
- Studies should use NBS and robotic therapy in combination;

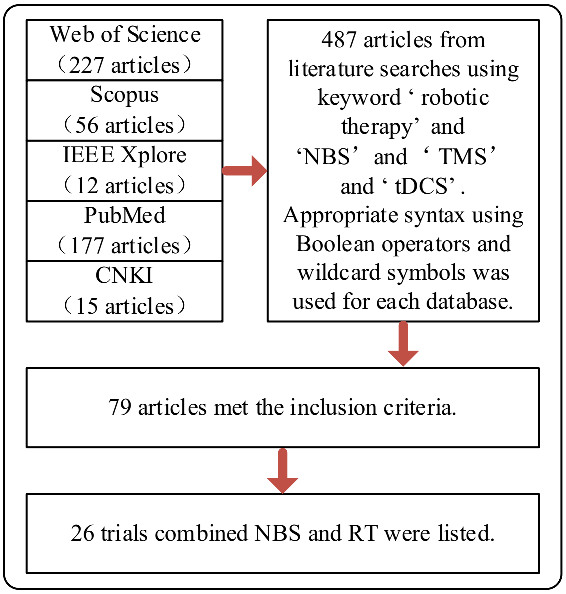
2.3 Exclusion Criteria

- Studies that lacked peer review or solely provided protocol descriptions;
- Studies that fulfilled the inclusion criteria but did not have outcomes due to an absence of response from the author;
- Studies focused on patients with motor dysfunction resulting from other diseases such as Parkinson's disease or amyotrophic lateral sclerosis.

Regarding the process of selecting references, following the mentioned inclusion and exclusion criteria, a thorough screening was conducted to eliminate irrelevant studies. Among the remaining articles, potentially eligible studies were considered for further evaluation if the full text was accessible.

2.4 Data Extraction

An overview of the article selection process is illustrated in Figure 1. Data extraction was conducted by two researchers, focusing on various parameters related to the intervention (tDCS or rTMS) and control groups. These parameters included the number of participants, time since onset, severity, motor function at baseline, training period and protocol, robotic



487 articles from literature searches using keyword ‘robotic therapy’ and ‘NBS’ and ‘TMS’ and ‘tDCS’. Appropriate syntax using Boolean operators and wildcard symbols was used for each database.

79 articles met the inclusion criteria.

26 trials combined NBS and RT were listed.

Figure 1 Flow diagram of the literature search and results setting, and outcome measures. The quality assessment of the studies, based on the inclusion and exclusion criteria, was performed using the Physiotherapy Evidence Database (PEDro) scale. Any inconsistencies between the results of the two researchers were resolved through discussions with a third researcher.

Relevant information on the study design, intervention, methods, and efficacy reporting of the combined approach involving NBS and robotic therapy was extracted from the chosen articles among those selected. This data extraction aimed to provide valuable insights into the outcomes and impacts that could be applied in clinical settings.

2.5 Results

The final search queries for this review were concluded in July 2023, resulting in the identification of 487 records through the research methodology. Following the screening of titles and abstracts, 408 articles were excluded as they did not meet the predetermined inclusion criteria. Consequently, 79 articles underwent eligibility assessment. Analysis of various scientific databases revealed that the majority of these 79 articles were published within the last decade, as depicted in Figure 2. After a thorough review of the full texts, 26 trials were included in the qualitative analysis of this review, as outlined in Table 1. With the exception of one clinical pilot trial, all included studies were randomized controlled trials (RCTs), including three pilot RCTs. Some trials focused on specific stimulation sites (e.g., cerebellum or spinal cord), timing (before, during, or after robotic therapy), and stimulation types (rTMS and tDCS). Additionally, variations were observed in double-blind design elements such as concealment allocation, blinding of outcome assessment, participants, and personnel.

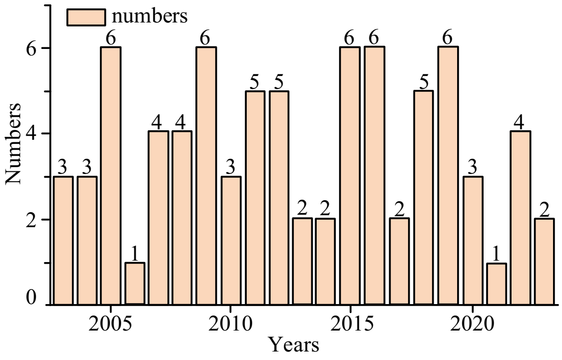


Figure 2 Number of the selected publications on the combined strategy of NBS and robotic therapy from January 2003 to July 2023

3 Non-invasive Brain Stimulation (NBS)

Invasive brain stimulation (IBS) refers to a therapeutic approach that involves the surgical implantation of electrodes or other stimulating devices directly into specific regions of the brain to modulate neural activity. This technique is primarily used for treating neurological and psychiatric disorders that are resistant to conventional treatments. Deep Brain Stimulation (DBS) is the most common IBS rehabilitation. Compared with invasive brain stimulation, NBS uses a non-invasive, non-traumatic method to stimulate the cerebral cortex and modulate its excitability. The non-invasive neural stimulation techniques usually include various forms, such as auditory, visual, electrical, magnetic, etc. In rehabilitation practice, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are the most commonly used NBS intervention.

3.1 rTMS Technique

TMS is a technique used to modulate neuronal excitability by applying a high-intensity magnetic field to the underlying brain tissue beneath the magnetic coil [3]. This magnetic field is generated when brief electrical currents pass through the coil, as shown in Figure 3. In 1985, Barker magnetically stimulated superficial peripheral nerves and recorded action potentials in nearby muscles, which was considered as the beginning of the TMS technique [4]. The earliest single-pulse and paired-pulse stimulations could depolarize cerebral cortex neurons and produce motor-evoked potentials (MEPs) in the motor cortex. Based on these characteristics, TMS is employed to assess neurological disorders and neurophysiological changes by measuring the cortical excitability thresholds and motor nerve conduction currents. Subsequently, rTMS and the theta-burst stimulation (TBS) are proposed. Both two technologies use a magnetic field to stimulate specific areas of the brain, but the stimulation patterns are different. rTMS delivers magnetic pulses at a fixed frequency (1–20 Hz), while TBS uses a high frequency (50–100 Hz) and short-duration magnetic bursts (less than 1 s). TBS includes a continuous theta-burst stimulation (cTBS) and an intermittent theta-burst stimulation (iTBS).

The pulsed magnetic fields used in the rTMS can alter the membrane potential of cortical neurons, produce induced currents, and regulate cerebral metabolism and neural electrical activity, resulting in a sequence of biochemical and physiological responses. Currently, the rehabilitation theories of rTMS mainly include

Table 1 Conclusions and comparisons of the different combined strategies

Author	Study design	Group 1		Group 2		Group 3		Outcome measure
		RT device	**NBS parameters**	**RT device**	**NBS parameters**	**RT device**	**NBS parameters**	
Hu [10]	RCT	Upper limb robot ArmGuider	1 Hz, 80%RMT, M1, 5 days/week, for 4 weeks	\	1 Hz, 80%RMT, M1, 5 days/week, for 4 weeks	\	\	WMFT FMA/MBI
Miller [74]	RCT	Wrist exoskeleton RW	5 Hz, 80%RMT, M1	Wrist exoskeleton RW	Sham stimulation	\	\	MVC TCI FMA
Lazzaro [76]	RCT	Shoulder-elbow robot InMotion2	50 Hz, 80%AMT, M1, 2 weeks	Shoulder-elbow robot InMotion2	Sham stimulation	\	\	FMA MA MD
Kumru [77]	RCT	Lower limb robot Lokomat	20 Hz iTbs, 90%RMT, 5 days/week, for 4 weeks	Lower limb robot Lokomat	Sham stimulation	\	\	UEMS LEMS
Chang [78]	SBPCPG	Hand robot SuperLabPro	10 Hz, 80% RMT, M1, for 10 days	Hand robot SuperLabPro	Sham stimulation	\	\	MA MT JHFT
Tian [79]	RCT	Gait training robot G-EO	10 Hz, 80%RMT, M1, 6 days/week, for 4 weeks	\	10 Hz, 80%RMT, M1, 6 days/week, for 4 weeks	Lower limb robot GEO	\	FAC BBS BI
Luo [80]	RCT	Lower limb robot Zhuo Dao	12 Hz, 80%RMT, M1, 6 days/week, for 4 weeks	Lower limb robot Zhuo Dao	Sham stimulation	\	\	CBIT FMA ADL
Buetefisch [81]	RCT	Upper limb robot Raha-Stim	0.1 Hz, 120%MT, M1, for 4 weeks	\	0.1 Hz, 120%MT, M1, for 4 weeks	Upper limb robot Raha-Stim	Sham stimulation	MT COG MEP SICE
Lin [83]	RCT	Upper limb robot Fourier M2	1 Hz, 110%RMT, M1, 5 days/week, for 4 weeks	\	1 Hz, 110%RMT, M1, 5 days/week, for 4 weeks	Upper limb robot Fourier M2	\	UFMA MBI FTHUE-HK
Kim [84]	RCT	Upper limb robot FourierM2	1 Hz, 110%RMT, M1, 5 days/week, for 4 weeks	\	1 Hz, 110%RMT, M1, 5 days/week, for 4 weeks	Upper limb robot Fourier M2	Sham stimulation	MVPT CBS K-MBI
Zhang [85]	RCT	Upper limb robot ArmMotus HandyRehab	70% RMT iTBS+ cTBS, M1, 3 days/week, for 4 weeks	Upper limb robot ArmMotus HandyRehab	70% RMT iTBS, M1, 3 days/week, for 4 weeks	Upper limb robot ArmMotus HandyRehab	Sham stimulation	UFMA MBI ARAT
Zhang [87]	RCT	Upper limb robot Fourier M2	1 Hz, 100%RMT, M1, 5 days/week, for 2 weeks	Upper limb robot Fourier M2	Sham stimulation	\	\	FTHUE-HK FMA
Edwards [88]	CPS	Wrist robot MIT-MANUS	a-tDCS, 1 mA, M1, 20 min	\	\	\	\	MEP SICI MVIC
Geroin [89]	Pilot RCT	Gait training robot GT1	a-tDCS, 1.5 mA, 5 days/week, for 2 weeks	Gait training robot GT1	Sham stimulation	\	\	6MWT 10MWT
Naro [90]	RCT	Gait training robot LokomatPro	dstDCS during the first 10 min of RAGT, 6 days/week, for 8 weeks	Gait training robot LokomatPro	dstDCS after RAGT, 6 days/week, for 8 weeks	Gait training robot LokomatPro	dstDCS before RAGT, 6 days/week, for 8 weeks	6MWT 10MWT

Table 1 (continued)

Author	Study design	Group 1		Group 2		Group 3		Outcome measure
		RT device	NBS parameters	RT device	NBS parameters	RT device	NBS parameters	
Hesse [92]	RCT	Upper limb robot Bi-Manu Track	a-tDCS, 2 mA, M1 of the affected hemisphere, 5 days/week, for 6 weeks	Upper limb robot Bi-Manu Track	a-tDCS, 2 mA, M1 of the unaffected hemisphere, 5 days/week, for 6 weeks	Upper limb robot Bi-Manu Track	Sham stimulation	FMS MAS BBT
Mazzoleni [93]	SBPCPG	Wrist robot InMotion	a-tDCS, 2 mA, M1, 5 days/week, for 6 weeks	Wrist robot InMotion	Sham stimulation	\	\	FMA BBT MAS/w
Triccas [94]	RCT	Upper limb robot Armeo$^{®}$Spring	a-tDCS, 1 mA, M1 2 days/week, for 8 weeks	Upper limb robot Armeo$^{®}$Spring	Sham stimulation	\	\	FMA ARAT
Danzl [95]	RCT	Gait training robot Lokmat	a-tDCS, 2 mA, M1, 3 days/week, for 4 weeks	Gait training robot Lokmat	Sham stimulation	\	\	10MWT BBS FAC
Picelli [96]	RCT	Gait training robot G-EO	c-tDCS over the CL, cerebellar hemisphere + cathodal tsDCS, 5 days/week for 2 weeks	Gait training robot G-EO	c-tDCS over the IL cerebellar hemisphere + cathodal tsDCS, 5 days/week for 2 weeks	\	\	6MWT AS FAC
Dehem [97]	RCT	Upper limb robot REAplan	dtDCS, 1 mA, M1, +sham stimulation	Upper limb robot REAplan	Sham stimulation + dual-tDCS, 1 mA, M1	\	\	BBT PPT
Seo [98]	Pilot RCT	Gait training robot Walkbot-S	a-tDCS, 2 mA, M1, 5 days/week, for 2 weeks	Gait training robot Walkbot_S	Sham stimulation	\	\	6MWT 10MWT BBS FAC
Ang [99]	RCT	Upper limb robot MIT-MANUS	btDCS, 1 mA, M1, 5 days/week, for 2 weeks	Upper limb robot MIT-MANUS	Sham stimulation	\	\	FMA EEG
Leno [100]	RCT	Gait training robot Lokmat	a-tDCS, 2 mA, leg motor cortex area, 5 days/week, for 4 weeks	Gait training robot Lokmat	a-tDCS, 2 mA, hand motor cortex area, 5 days/week, for 4 weeks	Gait training robot Lokmat	\	10MWT FAC
Ochi [101]	Pilot RCT	Upper limb robot Bi-Manu-Track	a-tDCS, 1 mA, M1, 5 days/week, for 1 week	Upper limb robot Bi-Manu-Track	c-tDCS, 1 mA, M1, 5 days/week, for 1 week	\	\	FMA MAS MAL
Straudi [102]	RCT	Upper limb robot Reo	btDCS, 1 mA, M1, 5 days/week, for 2 weeks	Upper limb robot Reo	Sham stimulation	\	\	FMA-UE BBT MAL

RT: Robotic Therapy; SBPCPG: Single-Blind Placebo-Controlled Parallel Group Trial; MVC: Maximum Voluntary Contraction; TCI: Transcallosal Inhibition; MA: Motion Accuracy; MD: Movement Duration; UEMS: Upper Extremity Motor Score; LEMS: Lower Extremity Motor Score; MT: Movement Time; JHFT: Jebsen Hand Function Test; CBIT-HK: Hong Kong Version of China Behavioral Inattention Test; ADL: Activities of Daily Living; MT: Motor Threshold; COG: Center of Gravity; SICE: Short Interval Cortical Excitability; MVPT: Motor Free Visual Perception Test; CBS: Catherine Bergego Scale; K-MBI: Korean Version of the Modified Barthel Index; UFMA: Upper Limb Fugl Meyer Motor Function Assessment; ARAT: Action Research Arm Test; FTHUE-HK: Hong Kong Version of Hemiplegic Upper Limb Function Test; BBT: Box and Block Test; MAS/w: Modified Ashworth Scale on the wrist; AS: Ashworth scale; PPT: Purdue Pegboard Test

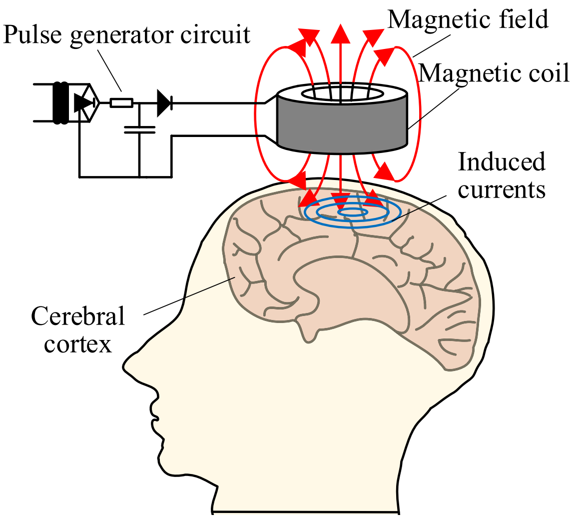


Figure 3 Stimulation principles of TMS

interhemispheric callosal inhibition, compensatory, and synaptic plasticity theories.

The interhemispheric callosal inhibition theory is the interhemispheric inhibition of physiological states between the two cerebral hemispheres through the corpus callosum, achieving and maintaining a balanced functional state. An increase in the activity level in one cerebral hemisphere will decrease that of the other to prevent signal interference from the two hemispheres and ensure the dominant role of a certain function [5]. In other words, the primary motor cortex (M1) of one hemisphere usually restrains that of the other [6]. The affected hemisphere of a stroke patient is inhibited due to its own hemisphere's nerve damage and the increased excitability of the healthy M1 area. Hence, a high-frequency (HF) stimulation is applied to the affected side to enhance its excitability, and a low-frequency (LF) stimulation on the healthy side to inhibit the activity of specific cortical areas, causing temporary and reversible virtual damage to the local brain function [7]. The excitability reduction of the healthy side and the inhibition decrease of the affected one can promote neurorehabilitation and restore the function of paralyzed limbs [8].

The compensatory theory suggests that the neural conduction of the damaged area is disrupted which affects the motor function of the corresponding limb. The adjacent area and the healthy hemisphere will form a new compensatory circuit to restore the damaged limb function. When the cortical representation area for hand movement of monkeys is ischemic damage, the hand function can be transferred to the adjacent intact cortical area [9]. Brain plasticity has emerged and verified by numerous experimental studies [10–12]. rTMS can regulate the cortical blood supply in the target area, promote the peripheral nervous compensation and the brain-derived neurotrophic factor (BDNF), improve the reconstruction of the neural cortex, and thus facilitate the recovery of neurological and motor functions.

Neuroplasticity, also known as brain plasticity or neural plasticity, refers to the brain's ability to reorganize itself by forming new neural connections in response to learning, experience, or injury. This phenomenon demonstrates the brain's remarkable ability to adapt and change throughout life. Neuroplasticity occurs at various levels, including synaptic plasticity, structural plasticity, functional plasticity, cross-modal plasticity, and use-dependent plasticity. Neuroplasticity is a fundamental process underlying learning and memory, recovery from brain injuries, and adaptation to changes in the environment. The relationship between synaptic plasticity theory and neuroplasticity lies in the fact that synaptic plasticity is one of the key mechanisms underlying neuroplasticity. Changes in synaptic strength and connectivity contribute to the brain's ability to adapt, learn, and rewire itself in response to various stimuli and experiences. Essentially, synaptic plasticity serves as a fundamental process through which neuroplasticity occurs, enabling the brain to change and adapt in response to internal and external factors. The synaptic plasticity theory believes that the reorganization of the connections among neurons can promote the recovery and improvement of brain function. Long-term potentiation (LTP) and long-term inhibition (LTD) are two main forms of synaptic plasticity. LTP is the phenomenon in which the efficiency of synaptic transmission among neurons is enhanced when the neurons are repetitively stimulated over a period of time. Comparatively, LTD weakens the strength of a synaptic connection when the neurons are not stimulated. LTD plays a role in the regulation of neural networks as it can eliminate unnecessary connections and optimize efficiency [13]. LTP/LTD effects can be induced by rTMS [14].

Various stimulation parameters of TMS are closely related to the rehabilitation effect where the critical parameters are the intensity, frequency, duration, and interval [15]. The stimulation intensity is the magnitude of the magnetic field applied to the cerebral cortex. Due to individual differences, it's necessary to determine the patient's motor threshold (MT) in the clinic [16]. An electrode is placed on the target muscle and the contralateral M1 is stimulated for 10 trials using TMS. The minimum intensity is the resting motor threshold (RMT) when no less than 5 MEPs (≥ 50 μV) are detected. The active motor threshold (AMT) is similar to RMT but differs in that AMT requires the volunteers to actively conduct a muscle contraction to determine the minimum stimulus intensity required to trigger a visible motor response. MT, generally replaced by RMT, is taken as a reference value for the intensity where the common intensity is 80%–120%MT. The stimulation frequency is the number of pulses per second. LF is less than or equal to 1 Hz, while HF is higher than 1 Hz. The HF stimulation can increase the cortical excitability at an appropriate intensity, whereas LF will decrease the excitability [17]. Continuous stimulation is commonly used in the LF-rTMS and duration is the whole period of the stimulation. The HF-rTMS utilizes the stimulation chain with a number of pulse strings and the duration is the period of each string [18].

rTMS apparatuses mainly consist of a pulse generator circuit and a magnetic coil. The magnetic coil directly influences the stimulation intensity, focalization, and depth. The earliest coils were circular, followed by the 8-shaped coils with higher focalization. The two coils have been applied to most TMS apparatuses. In recent years, new coil structures have been developed, such as quatrefoil coil, H-coil, and slinky coil (inspired by the structure of the toy Slinky).

The research on TMS has started earlier abroad and many companies have mature equipment development technologies. The famous equipment manufacturer, MagStim (formerly known as Novametrix Medical Systems Inc.), successfully promoted TMS technology based on the research of pioneers such as Anthony Barker, Reza Jalinous, and Mike Polson. MagStim developed the TMS prototype (Novametrix Model 200) in 1987 and obtained the first FDA certification. The current products mainly include Horizon, Rapid, BiStim, etc. However, Chinese research teams entered the TMS field relatively late. In 1988, Liao from Tongji Hospital of Huazhong University of Science and Technology successfully developed the first simple transcranial magnetic stimulation device in China that can be used for clinical testing [19]. Since there existed problems with slow charging speed and overheating of the coil during long-term use, this device had not been officially put into clinical application. Yiruide Group developed the first rTMS device with 100 Hz in 2008 and the advanced versions NS, MagTD, CCY, etc.

As an important rehabilitation technology for post-stroke movement disorders [20], rTMS has gained broad utilization in the diagnosis of neurological conditions and disorders, including Parkinson's disease, depression [21], and dyskinesia [22]. The LF-rTMS for the healthy M1 area and the HF-rTMS for the affected M1 area were recommended grade A and B to improve hand function in subacute stroke patients, respectively, in the latest European clinical practice guidelines [23]. Emara et al. [24] applied 1 Hz and 5 Hz rTMS to the healthy and affected M1 respectively and surveyed the long-term effects on the motor function and disability level. Both the Fugl-Meyer Assessment (FMA) and the Barthel Index (BI) increased significantly after 12 weeks of treatments, and the HF-rTMS possessed better therapeutic effects. Chang et al. [25] designed a placebo-controlled trial to assess the long-term effects of HF-rTMS on post-stroke dyskinesia and found that the subacute stroke patients achieved fine motion recovery, especially in squatting and walking. Yozbatiran et al. [26] treated stroke patients with HF-rTMS for 4 weeks and the motor function of the experimental group was improved significantly. In addition, no significant disparities were noted between the experimental and the placebo groups in terms of behavioral responses, cognitive function, and emotional state. For subacute stroke patients, Naoki et al. [27] applied HF-rTMS on the hand function area of the cerebral cortex and combined with occupational therapy for the upper limb. This combined treatment could effectively improve the upper-limb motor function and self-care ability in daily life. The cortical activities observed in the functional near-infrared spectroscopy(fNIRS) images were also enhanced markedly.

3.2 tDCS Technique

TES is an NBS technique in which the electric current penetrates through the cranium and acts on the cerebral cortex to modulate cortical excitability, as shown in Figure 4. The earliest TES was performed by placing electrodes on the scalp and applying high-voltage electricity. Most currents flowed along the scalp, only a small portion of the currents penetrated the outer tissues, acted on the brain, and activated neurons. Due to the significant discomfort and side effects, new types of TES have been developed which mainly consist of transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS). tDCS generally uses 1–2 mA of current and doesn't cause significant discomfort. In addition, the tDCS stimulator

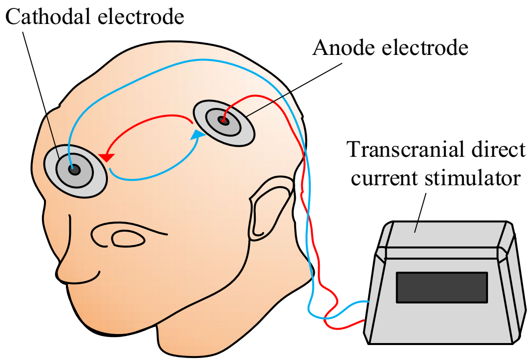


Figure 4 Stimulation principles of TES

is simple and easy to use. Hence, tDCS has become the mainstream choice of TES.

tDCS consists of three types of stimulation: anodal tDCS (a-tDCS), cathodal tDCS (c-tDCS), and sham tDCS. The first two techniques can enhance and diminish the cortical excitability of stimulated areas, respectively. The sham tDCS is usually used in the control group, which provides similar skin sensations but does not cause changes in the neuroexcitability [28]. Various molecular mechanisms are responsible for mediating the neuromodulatory effects of tDCS, including calcium-dependent alterations [29], the involvement of n-methyl d-aspartate receptors [30], the role of brain-derived neurotrophic factors [31], and the modulatory effects of tyrosine receptor kinase B [32] and γ-aminobutyric acid [33]. Notably, the after-effects of a single stimulation of tDCS can reach one hour and can endure for days or even months following multiple stimulations [34].

tDCS apparatus consists of a constant current generator, two electrodes, and an output control unit which are mainly manufactured by the two companies Neuroconn and Soterix Medical. During the clinical application, one electrode is placed above the cranium of the target location and the other electrode in the opposite orbit, shoulder, or extracranial location. The flow of electric current travels from the anode to the cathode, creating a complete circuit. The performance of tDCS is determined by the polarity of the electrodes, electrode size, sticking position, current density, current intensity, stimulation duration, and characteristics of the stimulated tissue [35]. The current intensity and stimulation duration are the main regulatory parameters. tDCS generally has a high safety when the stimulation duration is within 30 min and the current intensity is set to 1.0–2.0 mA [36].

a-tDCS has been widely applied to enhance cognitive functions (memory, language fluency, learning ability, etc.) [37], epilepsy [38], depression [39], aphasia [40], and addiction [41]. Particularly, the two stimulation modes, applying a-tDCS and c-tDCS to M1 areas of the affected and healthy sides respectively, have positive effects in the rehabilitation of post-stroke dyskinesia. Yasaroglu et al. [42] utilized the two modes to stimulate the affected sides to explore their effects and completed the flexibility tests of the affected hand before and after each stimulation trial. It was found that c-tDCS had no significant effect on the excitability of the M1 area. However, the M1 excitability after a-tDCS was improved by relieving the intracortical inhibition on the affected side. The recovery of hand motor function is a major challenge in post-stroke rehabilitation. Hummel et al. [43] applied a-tDCS (1 mA) to the affected M1 area, resulting in a significant improvement in hand function test scores. Kim et al. [44] investigated the effects of a-tDCS (1 mA) on the motor performance of paralyzed hands in subacute stroke patients. The block-box test and the finger acceleration measurement were conducted before, during, 30 min, and 60 min after the stimulation period, to assess the time-dependent changes in the motion performance. The experimental results demonstrated that a-tDCS significantly improved the performance of the finger acceleration and the block-box test, and the effects could last for 30 min and 60 min, respectively. Hesse et al. [45] applied the a-tDCS (1.5 mA) on the affected M1 areas of ten stroke patients. The arm functions of three patients were ameliorated prominently, whereas the improvements of the rest seven patients were not statistically significant. Nair et al. [46] employed c-tDCS (1 mA) on the M1 area of the healthy hemisphere and significant improvements were observed in the range of motion, and scores on neurological and motor function tests. Fregni et al. [47] conducted a cross-over controlled trial with a-tDCS on the affected hemisphere, c-tDCS on the healthy hemisphere, and a sham control group. The results revealed significant improvements in the scores of the hand function tests for the first two groups. These improvements were further validated with the help of TMS, which indicated a correlation between enhanced range of motion and reduced excitability in the contralateral hemisphere.

3.3 Comparison of rTMS and tDCS

Both rTMS and tDCS can effectively enhance neuroplasticity, increase cortical excitability, and facilitate the rehabilitation of motor functions. Benefitting from their immediate effects and after-effects, numerous scholars and therapists have combined the two techniques with other rehabilitation methods to create new ideas and approaches for rehabilitation strategies. Clinical reports have shown that the two techniques all have high safety and only isolated cases report adverse reactions such as skin discomfort, headaches, and induced seizures [48].

tDCS typically involves the application of a gentle direct electrical current (1–2 mA) through electrodes placed on the scalp. This method modifies the resting potential of neuronal membranes in a polarity-dependent manner, leading to increased or decreased excitability of neurons in a specific region [49]. rTMS applies a pulsed current passed through a coil placed above the scalp to produce a time-varying magnetic field. This magnetic field penetrates the scalp and skull to reach the target cerebral cortex and generate an induced current [16]. Due to their different underlying mechanisms, tDCS only affects neurons in an active state and cannot stimulate dormant neurons [50]. In addition, tDCS only induces local currents in neurons and does not elicit the spontaneous discharge of neurons. However, rTMS can induce action potentials in neurons. Both rTMS and tDCS are used to treat motor dysfunction in stroke patients. Besides, rTMS is also utilized for diagnosing neural pathway integrity [51]. tDCS exhibits higher safety, while rTMS possesses a better regulatory and promotive effect on impaired nerves.

During the tDCS treatment, there exists a slightly large region between the two electrodes, the current flows out along the path with the lowest resistance, and the partial current bypasses the target cortical region [52]. The coil magnetic field of rTMS exhibits significant attenuation in non-stimulation areas, indicating a high level of focalization. Compared with tDCS, rTMS has better spatial accuracy and strength stability [53]. From the view of clinical application, tDCS instruments are inexpensive, easy to use, portable, and can be combined with other rehabilitation techniques. rTMS devices are expensive, complex to use, and often require ancillary equipment such as positioning and navigation systems.

4 NBS Combined with Robotic Therapy

4.1 Principle of Combined Technique

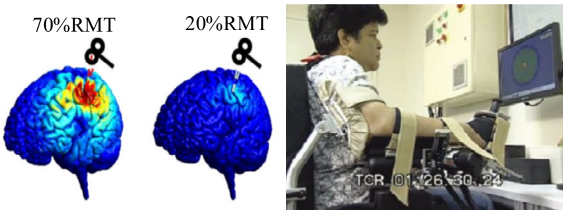
Post-stroke dyskinesia seriously affects patients' daily life and quality of survival. Rehabilitation treatment requires a substantial amount of manual labor and medical resources [12]. Currently, the main rehabilitation strategies are physiotherapy and occupational therapy, but there exist problems such as time-consuming, laborious, and dependent on the experiences of therapists. Therefore, the combination of NBS and robotic therapy paves the way for efficient rehabilitation methods. This combined technique can efficiently improve the neural plasticity, robustness, and durability of motor skill learning, which is superior to repeated passive or active assisted movements [11].

The application of robotics in therapy for individuals who have had a stroke shows great potential [54, 55]. It offers several advantages, including 1) enhancing the intensity and dose of physical exercises [56, 57], 2) enabling precise quantitative assessments of patients' recovery and treatment outcomes compared to traditional therapy [58, 59], and 3) creating an engaging and motivating environment that attracts patient participation [60, 61]. Numerous devices have focused on promoting rehabilitation for the entire arm, with a particular emphasis on the fingers and hand; however, it is important to allocate more attention to the rehabilitation of the wrist. The initial version of a wrist robotic system, integrated with the MIT-MANUS end-effector [62], was employed in robotic therapy. As a result, numerous researchers commenced the design and development of rehabilitation robots featuring either single or dual degrees of freedom (DoFs). A few of these researchers incorporated the forearm's pronation/supination as the third DoF within their mechanical structures [63, 64]. Pneumatic components, SMA muscles, or DC motors have been adopted in their drive units. Furthermore, both parallel and series mechanisms were employed to convert rotational or linear motions into singular or compound wrist movements. Some fully wearable exoskeletons enable patients to independently initiate recovery exercises, resulting in more frequent sessions [65, 66]. Flexible exoskeletons with outstanding compliance do not possess rigid supports, and the wrist bones are used as the support structure to transmit the power along the skin surface [67, 68]. This is particularly important since, in the future, more rehabilitation resources will be moved to community settings and patients' homes to conduct conventional therapy.

Robotic therapy, as an interdisciplinary technology of biomedicine and mechanical engineering, can provide continuous repetitions for limb movements. The trajectories, dynamic parameters, and interaction forces can be measured and analyzed with the help of sensors and artificial intelligence which will greatly improve the work efficiency of therapists [69]. Robotic therapy mainly provides four training modes: active, assistive, passive, and impedance training. In the active mode, the rehabilitation robots don't provide external assistance and only collect movement information. The robots will provide assistance for therapeutic exercises in the assistive mode. For paralytic patients, the passive mode is suitable since the robots can take upper/lower limbs to move along predetermined trajectories together. The impedance mode will enhance the muscle strength for patients without incomplete mobility. The assistive and passive modes can maintain and restore the range of motion of joints. In addition, the synaptic plasticity and connection can be improved through constantly learning and repeatedly using the affected limb which helps the recovery of limb functions [14]. The active and impedance modes are mainly used to improve the patients' motor function and promote the muscle strength of affected limbs.

However, robotic therapies have their own limitations, such as limitations in functional recovery. Rehabilitation robots can help patients with physical activity and exercise training, but they cannot directly influence the neurological repair process. The restoration of neural circuits requires a more complex and integrated treatment approach that includes medication, neurostimulation, and other rehabilitation methods. Rehabilitation robots usually rely on preset ranges of motion and strength to assist patients in motor training, but they lack immediate sensory feedback from the patient's body. In some clinical studies, rehabilitation robotics was not superior to enhanced upper extremity therapy (EULT) or usual

(a) InMotion 2 [63] (b) LF-rTMS [71]



(c) Intensity of stimulation [74] (d) MIT-MANUS [75]

(e) InMotion [80] (f) Armeo®Sprin [81]

Figure 5 NBS combined with robotic therapy

care. Lo et al. [70] conducted a study to assess the effectiveness of robot-assisted therapy in patients with long-term upper extremity dysfunction after stroke where this treatment lasted for 12 weeks and contained a total of 36 1-hour sessions. 127 patients were randomized into a robot-assisted therapy group, an intensive comparative therapy group, and a usual care group. The primary observation index was the improvement of motor functions at 12 weeks, and the secondary ones included the scores of the Wolf motor function test and the stroke impact scale. According to the findings, the group receiving robot-assisted therapy demonstrated significantly better stroke impact scale scores compared to the usual care group. However, there was no significant difference observed in FMA scores compared with the usual care and intensive comparative groups. Secondary analyses revealed significant improvements in the FMA scores and time taken to complete the Wolf motor function test at 36 weeks following robot-assisted therapy. Rodgers et al. [71] found that the combination of robot-assisted training and EULT did not yield improvements in upper limb functionality for patients with moderate or severe dysfunction. The outcomes did not endorse the utilization of robot-assisted training as administered in this particular trial.

NBS can modulate the excitability and inhibition of the M1 region [53], thereby promoting neuronal regeneration and reorganization to encourage the recovery of motor function. The precise motion control and force feedback assist paralytic patients in relearning the functions of upper/lower limbs and hands. The combination of NBS and robotic therapy will connect nerves and limb movements, superpose their respective advantages, and accelerate the rehabilitation effect [72]. The combined technique has been verified in many treatments of post-stroke dyskinesias [7, 35]. Unfortunately, the effectiveness of the same combined rehabilitation strategy varies significantly, due to the complexity and individual differences of the neural rehabilitation. It is necessary to analyze the combination methods, stimulation parameters, indicators, and rehabilitation effects, comprehensively. The parameters of the combined strategies are summarized in detail with their differences in Table 1.

4.2 Combination of HF-rTMS and Robotic Therapy

Both HF-rTMS and iTBS can increase the excitability of the cerebral cortex to promote learning ability, blood circulation, and plastic changes of the damaged and peripheral nerves [4]. Over 60% of stroke patients still cannot fully recover normal arm and hand functions despite receiving rehabilitation training, which is attributed to damage to muscle voluntary activation [73]. Miller et al. [74] designed a cross-over trial for the active extension of the wrist to analyze the effect of different rehabilitation methods on the voluntary activation of wrist extensors. This cross-over trial consisted of only robotic wrist training (RW), rTMS (5 Hz) for the ipsilateral M1 region, robotic training (rTMS + RW), and sham stimulation (Sham rTMS + RW). Compared with the Sham rTMS + RW, the recruitment thresholds of motor units significantly decreased and the emissivity modulation increased after rTMS + RW. Besides, the voluntary activation of wrist extensors was improved, but there was no increase in the two control groups. Further, there were no significant changes in the ipsilateral corticospinal excitability and the transcallosal inhibition for the control groups.

cTBS is a strong inhibitory rTMS mode and can induce LTD-like changes lasting for approximately an hour [75]. Based on previous research, Lazzaro et al. [76] designed a double-blind placebo-controlled trial to investigate the combined effects of cTBS (50 Hz) and robotic therapy in promoting cortical plasticity transfer of the affected hemisphere. Three pulses with the intensity of 80% AMT were applied to the affected hemisphere and repeated every 200 ms for a total of 600 pulses. Then the robotic therapy was performed immediately, as shown in Figure 5(a). The results showed that this method failed to promote the cortical plasticity transfer of the affected hemisphere with severe impairment, possibly due to the greater involvement of the healthy hemisphere in the recovery process. Therefore, inhibiting the excitability of the intact hemisphere may produce positive effects. Kumru et al. [77] developed a combination of iTBS (90% RMT) and a lower-limb robot Lokomat, and set a control group with the sham stimulation and Lokomat. They applied 2-s duration bursts of 20 Hz (40 pulses/burst) with intertrain intervals of 28 s, for a total of 1800 pulses over 20 min during the back-adjustment process prior to the gait training. Then, the gait rehabilitation was completed within 30 min after iTBS. It was found that the motor scores of the lower limb increased significantly and the upper limb function was also improved prominently after the combination training. In the follow-up, 71.4% of participants in the experimental group could successfully complete the 10-meter walking test (10MWT), compared with only 40% of the control group. In addition, in patients with neck spinal cord injuries, upper extremity motor improvement was also significantly greater in the real rTMS group than in the placebo rTMS group.

The combined rehabilitation strategies can promote cortical plasticity changes in many cases. However, the research on the neural recovery mechanism is not sufficient. Chang et al. [78] gave HF-rTMS (10 Hz) before the robot-assisted finger training and set a control group with sham rTMS to analyze the neural circuit of finger movements. The accuracy of finger movements was improved significantly in the experimental group. Furthermore, the motion performance of fingers was promoted by modulating the neural circuit of the cortico-basal ganglia-thalamus, with the help of functional magnetic resonance imaging. Tian et al. [79] conducted a randomized controlled trial to investigate the rehabilitative effect of HF-rTMS and an end-driven lower limb robot (G-EO). The experiments consisted of G-EO group, rTMS group (contralateral M1 region of lower-limb, 10 Hz, 80%RMT, stimulation 1 s, interval 3 s, 1200 pulses), G-EO+ rTMS group (first rTMS, 30 min interval, G-EO training for 20 min). The functional ambulation category (FAC), gait velocity (GV), berg balance scale (BBS), and modified Barthel index (MBI) were used to assess their walking ability, speed, balance function, and activities of daily living, respectively. The results showed that the FAC and BBS scores of the G-EO + rTMS group were higher than those of the other two groups. The combination strategy had a positive effect on the walking and balance abilities. Luo et al. [80] selected 90 stroke patients with unilateral spatial neglect and randomly divided them into a control group and an observation group with 45 cases respectively. In the control group, an upper-limb robot (ZD MedTech Co., Ltd, Dynaxis, China) was used for the rehabilitation training, while the observation group received additional rTMS treatment (80% MT, 12 Hz, once a day, 5 days/week, 4 weeks). The results showed that the combined strategy could enhance limb function and activities of daily living, and effectively improve the hemispatial neglect symptoms and the visual electrophysiological status.

4.3 Combination of LF-rTMS and Robotic Therapy

In the healthy state of cerebral physiology, the two cerebral hemispheres stay in a balanced physiological state of interactive inhibition through the corpus callosum. After a stroke, the inhibitory effect of the affected cortex on the healthy cortex is weakened. The competitive advantages of the healthy side prevent the expression of the remaining neural activities in the affected cortex which constrains the recovery of the affected side. LF-rTMS and cTBS can reduce cortical excitability. Therefore, the therapists usually apply LF-rTMS or cTBS to the healthy side to inhibit the excitability of the healthy cortex and weaken its inhibition on the affected side. The excitability of the affected side can be increased and the mutual inhibition between the hemispheres will be rebalanced. This is an important strategy of rTMS for post-stroke rehabilitation.

In the combined rehabilitation strategy, most studies have utilized either rTMS followed by robotic therapy or concurrent application of rTMS during robotic therapy. Buetefisch et al. [81] developed a transistor trigger circuit to ensure the temporal synchronization of rTMS and robotic therapy. During the trial, participants performed wrist movements (0.2 Hz) assisted by rehabilitation robots and LF-rTMS for the ipsilateral or contralateral M1 area (0.1 Hz, 80% RMT of the extensor carpi ulnaris muscle (ECU)). The transistor-triggered circuit generated a specific pulse to start the stimulation of LF-rTMS when the electromyographic (EMG) signal of ECU reached a predetermined threshold (10%–20% of the maximum MEP) [82]. The results demonstrated that the combined strategy was feasible for stroke patients and produced activity-dependent neural plasticity. The study revealed distinct effects on GABA-A-mediated inhibition and muscle map reorganization during training movements. Nevertheless, tDCS impacts on M1 of lesioned brains, such as after a stroke, exhibited differences relative to those noted in healthy participants with intact brains. Applying TMS to M1 in the support of training exercises led to a more focused increase in excitability. This was partly due to the ECU being active during TMS. The muscle activity decreased the MT of the corresponding M1, resulting in relatively high-intensity TMS for the targeted muscle.

For the majority of stroke patients, upper limbs are more prone to functional impairments compared with lower limbs, and the corresponding recovery is more challenging. The combined strategy of LF-rTMS (1 Hz) and the upper-limb robotic therapy had been verified to be safe and more efficient than a single treatment in three controlled trials [83]. However, the effect on daily life ability was not very obvious. Kim et al. [84] utilized robotic therapy and rTMS (0.9 Hz) for upper limb rehabilitation, as shown in Figure 5(b). Patients were induced to perform passive and active movements by integrating fun games. The combined strategy had better therapeutic effects compared with individual treatments alone. The scores of the evaluation indexes were higher than the other two single treatments, but the difference was not statistically significant. A similar experiment was conducted for two weeks [85], and the motor scores of upper limbs were higher than the control groups and the initial state, but the difference was also not statistically significant. Hu et al. [10] applied rTMS (1 Hz, 80% RMT) to the healthy M1 region, and then the upper limb robot ArmGuider was used to complete the rehabilitation training for 4 weeks. The experimental group exhibited a significant improvement in the motor abilities of the upper limbs.

rTMS has a cumulative effect on cortical excitability. Applying LF-rTMS to the healthy hemisphere will continuously weaken the inhibition on the affected side, and then applying HF-rTMS to the affected hemisphere will expand its effect on excitability. Tang et al. [86] first applied the LF-rTMS (1 Hz) on the healthy M1 area, then HF-rTMS (3 Hz) for the affected M1 area, and finally used a lower limb rehabilitation robot to assist the lower limb training. After 4 weeks of treatments, the experimental group exhibited significant improvements in motor function, balance function, and walking ability compared with the control group.

iTBS can increase cortical excitability and obtain similar effects to HF-rTMS, whereas its modulation time is short and there exist significant individual differences in the post-effects. The previous neural activity in the synaptic system is an adjustable factor for individual responses [17]. A prior low-level neural activity lowers the threshold and tends to induce long-term excitation. Conversely, a prior high-level neural activity raises the threshold and induces long-term inhibition. Based on this theory, Zhang et al. [87] applied cTBS and iTBS stimulations with different intensities on the healthy and affected hemispheres respectively, and then used an upper-limb robot to assist the rehabilitation training, as shown in Figure 5(c). The mirror visual feedback (MVF) and event-related desynchronization (ERD) of sensorimotor β oscillations induced by movement executions were selected as evaluation indexes. The results demonstrated that the combined approach generated better recovery outcomes for post-stroke hemiparesis, particularly in patients with better upper limb function.

4.4 Combination of tDCS and Robotic Therapy

tDCS can temporarily increase the cortical motor excitability of the hand's intrinsic muscles and enhance upper limb functionality in individuals with long-term stroke. Edwards et al. [88] combined tDCS with the rehabilitation robot MIT-MANUS for the hand function of post-stroke patients, as shown in Figure 5(d). TMS was used to measure the cortical motor excitability and the short-interval intracortical inhibition (SICI) before and after the combined rehabilitation training. After tDCS, there existed a significant increase in MEPs and remained significantly high level even after the robot-assisted training. This indicated that motor learning could coexist with the cortical motor excitability induced by tDCS, providing further support for the effectiveness of combined strategies in promoting neural recovery after the brain injury.

For lower limb recovery, a-tDCS can effectively increase the excitability of the corticospinal tract and reduce the excitability of the contralateral M1 region, which is due to the increased inhibitory effect of the interhemispheric corpus callosum. Geroin et al. [89] performed a randomized controlled trial for chronic stroke patients which combined tDCS with a lower limb robot to complete the gait training for two weeks. The scores of the 6-min and 10-m walk tests were improved significantly. Similar experiments adopted a dual-site transcranial direct current stimulation (dstDCS) combined with LokomatPro for gait training [90]. The experimental data suggested that it was better to apply the dstDCS before or during the training than after LokomatPro, particularly in gait stability, balance, and walking endurance. Previous studies have demonstrated the efficacy of combining a-tDCS with robotic therapy in the neural plasticity and the motor function of the upper limb [91]. Hesse et al. [92] designed a randomized double-blind controlled trial for patients with cortical involvement and severe weakness. a-tDCS (2.0 mA) and c-tDCS were applied to the affected and healthy sides respectively during the robotic therapy. A control group was added with sham tDCS. The experimental results showed that all three groups exhibited an increase in the FMA scores but without statistical differences.

The wrist motor function is an important part of the upper limb recovery. Mazzoleni et al. [93] combined tDCS with the wrist robot for subacute stroke patients, as shown in Figure 5(e). During the robot-assisted therapy, patients received a-tDCS (2 mA) where the anode electrode was positioned on the M1 region of the lesioned brain, while the cathode electrode was placed over the supraorbital bone of the opposite side After the combined training, both the movement speed and smoothness significantly increased. However, compared with the robotic therapy alone, the combined rehabilitation did not show any additional effects in subacute stroke patients. This could be attributed to the fact that the outcomes of tDCS were overshadowed by the effects generated by the high-intensity robotic training. In addition, an evaluation method based on the clinical scales and kinematics parameters could be used to evaluate the recovery of patients comprehensively. Partially combined strategies did not achieve satisfactory rehabilitation effects, possibly due to the robot-assisted training that solely focused on distal or bilateral upper limb movements. In order to address this limitation, Triccas et al. [94] incorporated a-tDCS into the three-dimensional and unilateral robot-assisted training for the upper limb impairment of subacute/chronic stroke patients, as shown in Figure 5(f). The training plan included 18 courses for 8 weeks and each course contained one hour of robot-assisted training. The robot provided sufficient three-dimensional motion workspace for comprehensive movements of the affected upper limb and grip strength. During the first 20 min of each session, a-tDCS (1 mA) was applied to the affected M1 region and sham tDCS in the control group. The results of the experiments showed that both the real and simulated treatment groups showed significant improvements in the clinical evaluation metrics (FMA, HPR, ARAT, MAL, and SIS) over time compared to baseline, but no statistically significant differences were observed between the real and control groups. The subacute group showed significant changes in several clinical evaluation metrics, while the chronic group showed less significant changes. This could mean that the intervention was more effective for the subacute patients and maintained some improvement at follow-up. However, for chronic patients, the effect of the intervention may have been relatively small. This study had limitations such as a small sample size, high heterogeneity, and differences in participant characteristics and concurrent treatments. These limitations may have an impact on the reliability and consistency of the study results.

tDCS was applied to the motor cortex of lower limbs and combined with a novel gait training to promote gait recovery in chronic stroke patients [95]. Feedback from patients and caregivers was utilized to provide guidance for future trial design. It was found that both the active and sham tDCS groups showed a trend of improvement, but the improvement was more significant in the former group. Picelli et al. [96] combined the contralesional cathodal transcranial direct current stimulation of the cerebellum (tcDCS) and cathodal transcutaneous spinal cord direct current stimulation (tsDCS) with the robot-assisted gait training separately for patients with chronic intracranial stroke, with the 6-min walk test (6MWT) as the primary assessment indicator. The results showed that the two groups obtained significant within-group improvement in the 6MWTs, but there was no significant difference at each assessment time point. The cerebellar tcDCS synergized with tsDCS had similar effects on the robot-assisted gait training in chronic intracranial stroke patients. The dual-transcranial direct current stimulation (dtDCS) was also combined with the robot-assisted rehabilitation [97]. Unfortunately, there were slight improvements in hand dexterity and arm movements, and the effect did not have clinical significance. Seo et al. [98] investigated whether tDCS could enhance the functional gait with Walkbot-S in 24 chronic stroke patients with impaired gait. The treatment group received Walkbot-S + a-tDCS and the control group Walkbot-S + sham tDCS. The primary index was FAC, and the secondary ones included various walking tests, balance assessments, and MEP parameters. Participants underwent assessments prior to the treatments, immediately after, and at a 4-week follow-up. The study observed notable enhancements in gait function and walking ability following tDCS interventions. Ang et al. [99] evaluated the effectiveness of bilateral transcranial direct current stimulation (btDCS) for motor recovery in stroke patients and explored its application in conjunction with the motor imagery brain-computer interface (MI-BCI) and robotic therapy. The experimental group received the btDCS intervention while the control group received a sham intervention. btDCS was applied to the brain to modulate its excitability, then a robotic device performed the affected arm movements based on the electroencephalogram (EEG) of the motor imagery, to provide positive feedback. Unfortunately, it was found that btDCS did not have a significant effect on motor recovery in stroke patients. Leon et al. [100] explored the feasibility of combining btDCS with robot-assisted gait training and investigated the effect of btDCS on walking ability in subacute stroke patients. The enhancing effect of btDCS on the robot-assisted gait training was assessed through established three groups: btDCS for the motor cortex of the lower limb and hand, and no btDCS. Functional assessments, including 10MWT and FAC, were performed during the 4-week training period. Although there existed significant improvements in the gait speed and FAC in all three groups, the performance of the first group was not superior to that of the rest two groups.

Although the combination of robot-assisted arm training (AT) and tDCS is expected to provide some clinical benefits, the difference in tDCS effectiveness of the affected and unaffected hemispheres in patients with chronic stroke is still unclear. Ochi et al. [101] conducted a crossover, double-blind study of the hemiplegic arm by applying a-tDCS to the affected hemisphere + AT and c-tDCS to the unaffected hemisphere + AT, and investigated the efficacy of the combination therapy. The trial included 18 chronic stroke patients with moderate to severe upper extremity paralysis. Each patient received both the two treatments and each intervention lasted for 5 days. The results suggested that combination therapy had achieved limited outcomes in chronic stroke patients. tDCS polarity had different influences on the distal spasticity, and c-tDCS on the unaffected hemisphere improved spasticity better than a-tDCS on the affected hemisphere for patients with right hemisphere damage. Straudi et al. [102] proposed the combination of bilateral tDCS and robotic-assisted therapy in stroke patients and examined the effects of stroke duration and type on treatment outcomes. Based on the influences of these factors, a more individualized and effective approach for motor recovery could be provided. Chronic and subcortical strokes could obtain more improvement than acute and cortical strokes benefiting from the combination therapy.

5 Discussion

With the development of the motor relearning theory and neuroplasticity in clinical trials, neural rehabilitation techniques have gradually been applied to clinical practices. Especially, rTMS and tDCS techniques have made a great achievement. NBS and robotic therapy possess similar underlying principles in neural rehabilitation, and their combined strategy is widely regarded as a promising research direction. Based on the neural stimulation and repetitive limb movements, the combined strategy helps post-stroke patients regain muscle functions and a healthy nervous system faster and more accurately. In addition, objective indicators of both the nervous system and motor function can be obtained to assess the rehabilitation status. In most treatment cases, the combined therapy has demonstrated significant advantages over only using NBS or robotic therapy. During some upper limb rehabilitation, tDCS is selected as a substitute for rTMS to perform the robotic therapy simultaneously [103], benefitting from its stable position of electrodes. Additionally, tDCS offers a simpler procedure, lower equipment costs, and better cost-effectiveness. For lower limb rehabilitation, some researchers recommend the combined treatment of rTMS and robotic therapy, as the M1 region for the lower limb is located deeper in the cerebral cortex [48].

The rehabilitation models of NBS combined with robotic therapy covered in this review are summarized. The combined rehabilitation model primarily consists of two parts: the NBS rehabilitation mode and the rehabilitation robot mode. The NBS rehabilitation mode can be categorized into excitatory and inhibitory stimulation, and based on device parameters, it includes high-frequency rTMS stimulation, low-frequency rTMS stimulation, iTBS stimulation, cTBS stimulation, and more. The robot-assisted rehabilitation mode is divided into passive rehabilitation mode, active rehabilitation mode, and impedance-controlled rehabilitation mode based on the patient's force values. The combined rehabilitation mode can be viewed as permutations and combinations of different NBS rehabilitation modes and rehabilitation robot modes. It is worth noting that the selection of different rehabilitation modes depends on the specific conditions of the patient and the physician's diagnosis, and the choice of rehabilitation modes for the same patient may also vary at different stages of rehabilitation.

It was worth noting that in some studies [78, 92, 93], NBS combined with robotic therapy did not show statistically significant differences compared to using NBS or robotic therapy alone. It is our belief that one or a combination of three mechanisms may be at play here: (1) The various classification/severity of stoke patients and stimulation types/parameters (such as individual difference, therapeutic dose, stimulation polarity, and frequency) all can lead to different rehabilitation effects. (2) For some patients with mild or moderate strokes, significant rehabilitation outcomes can already be achieved by either robotic therapy or NBS. Therefore, the combined applications in these populations may result in overlapping effectiveness while failing to further improve treatment outcomes. (3) There may exist deficiencies within the experimental design, such as insufficient sample sizes, incomplete evaluation indexes, unreasonable group settings, unequal participant distribution. Future designs of combined rehabilitation trials should consider these factors more comprehensively.

The application order of NBS and the robotic therapy is another key content. It's a common choice to complete the NBS stimulation before or during the robotic therapy [76]. It is worth considering that some studies have employed a pre-stimulation before NBS to enhance the neuro-regulatory effects [81, 86, 87]. Similarly, the utilization of brain stimulation navigation systems and coil positioning devices allows better determination of the stimulation location which can improve the stimulation precision and enable simultaneous use of the two techniques [74].

In future developments, more rehabilitation intervention technologies (such as virtual reality, BC) may be integrated to leverage their respective advantages and create more effective and personalized interventions for various clinical and research applications. While NBS and BCI technology serve different purposes, there is potential for synergy between the two in future developments. The combination of NBS with BCI technology may offer new opportunities for enhancing neurorehabilitation outcomes in stroke rehabilitation or motor recovery after spinal cord injury. NBS could also be used to modulate neural activity in specific regions to enhance the efficacy of BCI systems, potentially improving the quality and reliability of brain signal detection and interpretation. Continued innovation in device technology may facilitate the development of portable, home-based NBS devices that allow patients to receive treatment outside clinical settings, improving accessibility and convenience. Advancements in neuroimaging and neurophysiological techniques may enable the development of personalized NBS protocols tailored to individual patients' brain connectivity and response characteristics.

For the significant inter-individual variability, further reliable evidence is needed to support the effectiveness of combination rehabilitation. We suggest expanding the sample size of randomized trials to reduce result bias and increasing the number of patients with the same etiologies and injury locations. Additionally, it is necessary to utilize a standardized approach for data analysis and evaluate the duration of therapeutic effects of tDCS and rTMS, as well as the long-term maintenance and prognosis of neural system improvement. Extensive clinical research is still required for the combined strategy to determine more efficient, reliable, and easily implementable stimulation and rehabilitation parameters. To achieve personalized adaptation for different patients in non-invasive brain stimulation rehabilitation, some challenges and potential strategies, such as inter-individual variability, real-time monitoring and feedback, novel devices and algorithms, could be considered to benefit neurological rehabilitation. Individuals vary widely in their brain structure, function, and response to interventions. Researchers can adopt a personalized medicine approach by tailoring interventions based on individual characteristics such as age, gender, genetics, cognitive abilities, and neurological condition. Machine learning and artificial intelligence (AI) techniques can analyze large datasets of physiological and behavioral signals to identify patterns, predict outcomes, and personalize interventions. These algorithms can learn from past data to optimize stimulation parameters, predict motor intentions, or adjust rehabilitation exercises based on individual patient characteristics and progress. Personalized adaptation requires continuous assessment of the patient's progress over time and adjustments to the intervention as needed. Longitudinal studies with follow-up assessments can track changes in motor function, cognitive abilities, and quality of life to optimize treatment strategies and long-term outcomes. Personalized adaptation also involves understanding the patient's preferences, goals, and motivation factors to enhance engagement and adherence to the intervention. Gamification, virtual reality, interactive feedback, and social support can be integrated into rehabilitation programs to make them more enjoyable, meaningful, and sustainable for patients.

6 Conclusions

rTMS and tDCS have been proven to effectively promote neurological rehabilitation. The high-intensity movement training of the robotic therapy has also shown promising rehabilitation outcomes. The combination of the two techniques has become a powerful supplement to the conventional treatment. It is worth noting that the combination strategy has made encouraging achievements for post-stroke movement disorders. Future research trends to focus on sample sizes, trial reliability, individual variabilities, common stimulation effects, efficient stimulation parameters, and order of both approaches. The combined strategy will become increasingly attractive for clinical applications and create boundless academic and social values for human health.

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Authors' Contributions

FR and JF were in charge of the whole manuscript; LZ and YC wrote the manuscript; YC and JF assisted with sampling and laboratory analyses. All authors read and approved the final manuscript.

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Availability of Data and Materials

Data will be made available on request.

Declarations

Competing Interests

The authors confirm that they do not have any conflicts of interest to disclose.

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