Narrative Review of Noninvasive Brain Stimulation in Stroke Rehabilitation

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Stroke is a disease with a high incidence and disability rate, resulting in changes in neural network and corticoid-subcortical excitability and various functional disabilities. The aim of the present study was to discuss the current status of research and limitations and potential direction in the application of noninvasive brain stimulation (NIBS) on post-stroke patients. This literature review focused on clinical studies and reviews. Literature retrieval was conducted in PubMed, Cochrane, Scopus, and CNKI, using the following keywords: Repeated transcranial magnetic stimulation, Transcranial direct current stimulation, Transcranial alternating current stimulation, Transcranial alternating current stimulation, Transcranial focused ultrasound, Noninvasive vagus nerve stimulation, Stroke, and Rehabilitation. We selected 200 relevant publications from 1985 to 2022. An overview of recent research on the use of NIBS on post-stroke patients, including its mechanism, therapeutic parameters, effects, and safety, is presented. It was found that NIBS has positive therapeutic effects on dysfunctions of motor, sensory, cognitive, speech, swallowing, and depression after stroke, but standardized stimulus programs are still lacking. The literature suggests that rTMS and tDCS are more beneficial to post-stroke patients, while tFUS and tVNS are currently less studied for post-stroke rehabilitation, but are also potential interventions.

Keywords: **Extracorporeal Shockwave Therapy • Stroke Rehabilitation • Transcranial Direct Current Stimulation • Transcranial Magnetic Stimulation • Vagus Nerve Stimulation**

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Background

Stroke, a common neurological disorder, occurs worldwide and has high mortality and disability rates [1,2]. Mortality rates have steadily declined due to recent advances in acute treatment and in primary and secondary prevention [3]. The irreversible brain damage caused by stroke leaves survivors with a permanent neurological deficit, causing serious dysfunction and affecting quality of life [2]. This causes a high demand for rehabilitation of stroke survivors.

Under normal circumstances, there is a functional balance between the 2 hemispheres of the brain, regulated by inter-hemispheric inhibition [4]. This equilibrium is affected after the stroke, with enhanced excitability in the contra-lesional hemisphere, while an abnormally increased interhemispheric inhibition occurs in the affected hemisphere [5,6]. Thus, it is of great importance to modify cortical excitability and adjust the balance between hemispheres for the rehabilitation of post-stroke patients [7]. In consequence, a potential strategy for rehabilitation is to modulate the plasticity by NIBS, including repeated transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial focused ultrasound (tFUS), and noninvasive vagus nerve stimulation (nVNS), seeking to restore the normal activity pattern [8-12]. Therefore, a detailed overview of the literature summarizing the current state of NIBS research is essential and valuable. This article presents a narrative review of previous research on NIBS in the treatment of post-stroke patients, including the mechanism, therapeutic parameters, effect, and safety.

Material and Methods

The following electronic databases were searched: PubMed, Web of Science, Elsevier, The Cochrane Library, and CNKI. The search strategy was developed using the following subject heading associating with stroke: Ischemic stroke, Hemorrhagic stroke, Repeated transcranial magnetic stimulation (rTMS), Transcranial direct current stimulation (tCDS), Transcranial alternating current stimulation (tACS), Transcranial focused ultrasound (tFUS), and Noninvasive vagus nerve stimulation (nVNS). We included articles on the rehabilitation of stroke patients using NIBS and related literature on NIBS mechanism, while those not related to the research topic were excluded. In addition, the references of the selected literature were also considered.

Results

We included 200 articles published from 1985 to April 2022 for analysis. Ten randomized controlled trials or clinical trials of rTMS in the treatment of stroke were selected, most of which stimulated the M1 area, but the stimulation frequency varied, and was mainly 1 Hz, 5 Hz, and 10 Hz. Nine clinical trials of tDCS for stroke were selected, most of which were randomized controlled trials, with a stimulation intensity of 1mA and 2mA and stimulation duration of 20 min. There were few studies about tACS in the treatment of stroke; only 3 articles were included, and the stimulation parameters varied. In addition, 3 randomized controlled trials of tFUS were chosen, and the stimulation site was the temporal window of the lesion side, and the frequency was 800 kHz, but the intensity varied. There were 6 clinical trial articles on tVNS for stroke, and the frequency used varied between 20 and 30 Hz, and the intensity was adjusted individually according to patients' tolerance.

NIBS for Post-Stroke Patients

Utilization of rTMS

In the late 20th century, Barker et al [13] discovered that it was possible to use TMS to stimulate both nerves and the brain. Since then, TMS has been widely used clinically. TMS, a noninvasive form of neurostimulation, uses electromagnetic induction to generate an electrical current in the brain and affects the electrophysiological activity of nerves [14]. A sufficiently strong induced current causes the neurons to depolarize, creating an action potential induced by TMS [15]. rTMS is a series of pulses that can alter and modulate cortical activity after the stimulation period, which has shown promising therapeutic potential in multiple neurological conditions [16]. In addition, rTMS can significantly reduce blood–brain barrier (BBB) permeability, improve vascular structure and morphology, and regulate cerebral perfusion [17]. Angiogenesis can be promoted and apoptosis of vascular endothelial cells can be reduced by rTMS [18].

Cortical excitability can be modulated by rTMS in a frequency-dependent manner. Low-frequency rTMS (LF-rTMS, ≤1 Hz) decreased cortical excitability, while high-frequency rTMS (HF-rTMS, >1 Hz) increased it [19-22]. Thus, rTMS can be used in both the affected and unaffected hemispheres [7,23]. Clinically, LF-rTMS was applied to the contralateral hemisphere to inhibit it, while HF-rTMS was used to stimulate the affected hemisphere to increase cortical excitability, thereby correcting excessive mutual inhibition between cerebral hemispheres after stroke and improving the function of patients [24-27]. 1 Hz LF-rTMS and 10 Hz HF-rTMS are mostly used clinically, and both have been proven to be safe and well tolerated [28]. Various protocols were utilized in clinical trials, as shown in **Table 1**.

Regarding targeted regions, different dysfunctions correspond to different brain regions. The most common site of stimulation was the primary motor cortex (M1), which was used to

Table 1. Summary of clinical studies on post-stroke patients using rTMS.

Study	No.	Targeted lesion	Study design	Interv-ention	Protocol design	Hemi-sphere	Loca-tion	Sche-dule	Follow-up	Outcome
Kondo et al, 2013 [21]	13	Spastic hemiparesis	CT	LF-rTMS	1 Hz (90% rMT)	Unaffected	M1	20 min, single	N/A	F-mean/M ratio decreased significantly in the affected upper limb
Cha et al, 2016 [25]	30 (15)	Subacute stroke with unilateral neglect	RCT	LF-rTMS vs sham	1 Hz (90% rMT)	Unaffected	Parietal	20 min for 20 d	N/A	Line bisection, Albert, Box and block, and Grip strength tests positive
Guan et al, 2017 [27]	42 (21)	Acute ischemic stroke	RCT	HF-rTMS vs sham	5 Hz (120% rMT)	Affected	M1	50 trains of 20 pulses for 10 d	1 mo, 3 mo, 6 mo, 1 yr	NIHSS, BI, FMA-UL positive for 1 mo, FMA-UL positive for 1 yr
Yang et al, 2017 [30]	60	Subacute stroke with unilateral neglect	RCT	LF-rTMS	1 Hz (90% rMT)	Unaffected	Parietal	900 pluses for 14 d	6 weeks	Behavioral Inattention Test positive
Sasaki et al, 2017 [26]	21 (11)	Hemispheric stroke lesion in the early phase	RCT	HF-rTMS	10 Hz (90% rMT)	Affected	M1	10 min twice a day for 5 days	N/A	BRS, ABMS II positive
Du et al, 2019 [22]	60	First-ever ischemic stroke	RCT	HF-rTMS	10 Hz (100% rMT)	Affected	M1	1200 pulses for 5 d	3 mo	FMA positive
				LF-rTMS	1 Hz (100% rMT)	Unaffected				
Ünlüer et al, 2019 [147]	30	Monohemi-spheric stroke	RCT	rTMS vs conventional	1 Hz (90% rMT)	Unaffected	M1	20 min for 5 d	3 mo	PAS, T-SWAL-QOL positive
Wang et al, 2019 [102]		Chronic stroke	RCT	HF-rTMS vs sham	5 Hz (90% rMT)	Affected	M1	15 min, 3 times a week for 3 weeks	1 mo	Gait performance, spatial asymmetry of gait, and motor function of the lower extremities positive
Hordacre et al, 2020 [29]	11	Chronic stroke with depression	RCT	HF-rTMS	10 Hz (110% rMT)	Affected	DLPFC	37.5 min for 10 d	1 mo	BDI positive
Zumbansen et al, 2022 [32]	28 (14)	Chronic versus subacute stroke	RCT	LF-rTMS vs sham	1 Hz (90% rMT)	Unaffected	Inferior frontal gyrus (Broca's area)	15 min, single	30 d	BNT, SF1min, TT, UnAS positive

NIHSS – National Institute of Health stroke scale; BI – the Barthel index of ADL; FMA – Fugl-Meyer Assessment; BRS – Brunnstrom Recovery Stages; ABMS II – Ability for Basic Movement Scale Revised; PAS – the Penetration-Aspiration Scale; T-SWAL-QOL – the Turkish version of The Swallowing Quality of Life; BDI – Beck depression rating scale; BNT – Boston Naming Test; SF1min – semantic fluency test (animals in 1 minute); TT – 36-item Token Test; UnAS – unified aphasia score.

treat motor dysfunction, spasm, and dysphagia [22,25,27]. rTMS has been applied to the contralateral dorsolateral prefrontal cortex (DLPFC) for post-stroke depression (PSD) and cognitive dysfunction [29]. For some post-stroke unilateral neglect patients, the parietal cortex was generally stimulated [30]. Stimulation of the Broca area was used to treat motor aphasia [31,32], and stimulation of the Wernicke area was applied for sensory aphasia [33]. However, large-scale alterations at the network level emerge after the plastic effects of rTMS, which contribute to local and long-term changes in the stimulated network and interactions between the stimulated and other functional networks [34,35].

Utilization of tDCS and tACS

Appropriately 20 years ago, as a noninvasive modulation of motor cortex excitability, tDCS was applied in humans [36]. tDCS generates a constant and weak direct electrical current (1-2 mA) by 2 or more electrodes placed on the scalp, which promotes neuroplasticity and modulates cortical excitability via subthreshold alternation of neuronal membrane potentials [37,38]. Moreover, Nitsche et al [36] found that cortical excitability and activity altered by tDCS depends on the current flow direction through the target neurons. The anode depolarizes the resting potential of the cell membrane and increases excitability of the cortex, while the cathode hyperpolarizes the resting potential and inhibits excitability of the cortex [36,39]. In addition, its effect is not limited to the stimulated region, but also involves nearby brain regions, which can change the functional connections between large brain regions [40]. tDCS has also been shown to improve local cerebral blood flow, which helps alleviate inflammation and protect neurons in ischemic areas [41].

The treatment parameters and duration determine the effect of tDCS. Wen et al [42] found that tDCS had intensity and time dependence in dose effect, which means high-intensity and long-duration stimulation has a better effect. However, this is not a general rule. Increased intensity of tDCS does not necessarily increase the efficacy of the stimulus, but may also shift the direction of excitatory changes [43]. Moreover, Jamil et al [44] demonstrated that the post-excitability effect was not linearly correlated with the increase in direct current intensity. Most relevant studies used 1, 1.5, and 2mA, and the treatment duration was mostly 20 min, as shown in **Table 2**. The area stimulated is important; benefits have been shown using anodic tDCS of the ipsilateral primary motor cortex (M1) and cathodic tDCS of the contralateral M1, as well as bi-hemispheric stimulation for the rehabilitation of dyskinesia [11,45]. Studies [46] have shown that placing the anode on the DLPFC of the affected side and the cathode on the superior orbital margin of the contralateral side can effectively reduce fatigue after stroke. In addition, stimulation of the Broca and the

Wernicke regions has been used in the treatment of aphasia after stroke, but its effectiveness remains uncertain [47,48].

Another transcutaneous electrical stimulation is tACS, with more than 10 years of application history. tACS affects cortical neurons by applying sinusoidal communication on the scalp, thus regulating brain oscillations to reshape internal brain rhythms and improve relevant brain functions [49]. As distinct from TMS, tDCS does not directly induce brain activity leading to a large-scale synchronous discharge of action potential, but rather alters the membrane potential and discharge threshold of neurons [50-52]. On the entrainment of endogenous neuronal oscillations, cortical excitability and activity-dependent are altered. By synchronizing the neural network, tACS alters the transmembrane potential, modulates the discharge frequency of neurons, and changes the oscillating rhythm of the brain [53,54]. Thus, tACS can specifically modulate oscillatory brain activity and selectively enhance oscillations at the applied stimulus frequency [55,56].

Stimulation conditions for tACS varied according to the frequency, site, and duration, as shown in **Table 3**. tACS at 70 Hz has been confirmed to temporarily enhance motor function, but whether it leads to long-term consolidation of motor learning remains to be studied [57]. It was previously demonstrated that 10 Hz and 20 Hz tACS improve motor sequence learning [58], but some studies have found that tACS has no effect on motor learning and can even be detrimental to motor consolidation [59]. The stimulation areas are also changed according to the lesion. Applying tACS to the primary motor cortex [58], the prefrontal cortex [60,61] and cerebellar cortex [62] can improve motor learning. Stimulation of the prefrontal cortex affects depression [63] and vision [64], and the parietal cortex is correlated with cognitive ability [65]. Wu et al [66] found that tACS over bilateral mastoids appears to improve functional recovery and cerebral hemodynamics in patients in the subacute phase of stroke. However, another study [67] of tACS stimulation for patients with hemianopia after chronic stroke found no significant improvement. There are few clinical studies [68] on tACS for post-stroke treatment, and new studies are needed.

Utilization of tFUS

While the modulation effects of rTMS, tDCS, and tACS are confined to the cortical surface, tFUS transmits ultrasound into deep brain regions [69,70]. tFUS can directly affect the ability of cells to discharge [71], and selectively stimulate and inhibit brain activity, thus modulating the excitability of neural tissues [72].

The commonly used tFUS includes high-intensity tFUS and low-intensity tFUS. High-intensity tFUS causes tissue damage through its thermal effects, thus blocking synaptic transmission

Table 2. Summary of clinical studies on post-stroke patients using tDCS.

Study	No.	Targeted lesion	Study design	Stimu-lation	Hemi-sphere	Location	Schedule	Follow-up	Outcomes
Bae et al, 2014 [121]	14 (7)	Central post-stroke pain	CT	2 mA	Affected (anode)	M1	20 min, 3 times per week for 3 weeks	N/A	VAS, skin temperature, the quantitative sensory test positive
Valiengo et al, 2017 [158]	48 (24)	Post-stroke depression	RCT	2 mA	Affected (anode); unaffected (cathode)	DLPFC	30 min for 10 sessions within 2 weeks	4 weeks	HDRS-17, MADRS positive
Koo et al, 2018 [122]	24 (12)	Subacute stroke	RCT	1 mA	Affected (anode)	The primary somatosensory cortex	20 min for 10 d consecutively	N/A	rNSA, MBI positive
Fridriksson et al, 2018 [133]	74 (34)	Long-term post-stroke aphasia	RCT	1 mA	Affected (anode); unaffected (cathode)	N/A	20 min for 15 sessions within 21 d	6 mo	Naming improvement
Suntrup-Krueger et al, 2018 [153]	60	Acute dysphagic stroke	RCT	1 mA	Unaffected	Swallowing motor cortex	20 min for 4 d	N/A	FEDSS positive
Feil et al, 2019 [48]	12	Post-acute non-fluent aphasia	RCT	2 mA	Bi-hemispheric	Inferior frontal gyrus (IFG)	20 min for 10 sessions within 2 weeks	4 weeks	Picture Naming Task, ANELT, AAT positive
Bolognini et al, 2020 [11]	32 (16)	Acute stroke	RCT	2 mA	Bi-hemispheric	M1	15 min for 10 sessions, 5 d	6 mo	MI-UL positive
Dong et al, 2021 [46]	60 (30)	Post-stroke fatigue	RCT	1.5 mA	Affected (anode); unaffected (cathode)	DLPFC	20 min per session, once a day, and 6 times a week	8 weeks	FSS, FMA, MBI positive
Muffel et al, 2022 [197]	24	Chronic hemiparetic stroke	RCT	1 mA	Bilateral-dual vs unilateral-anodal	M1 hand area	20 min	N/A	Bi-tDCS have better effects on sensorimotor functions post-stroke

VAS – Visual analogue scale; HDRS-17 – Hamilton Depression Rating Scale-17; MADRS – the Montgomery-Aberg Depression Rating Scale; rNSA – Revised Nottingham sensory assessment; MBI – the modified Barthel index; ANELT – Amsterdam Nijmegen Everyday Language Test; AAT – Aachen Aphasia Test; MI-UL – Motricity Index-upper limb; FSS – the Fatigue Severity Scale; FMA – Fugl-Meyer Assessment; MBI – Modified Barthel Index.

and inhibiting the electrical activity of neurons [73,74]. However, mechanical or thermal damage to tissue is likely to occur [75]. As a result, high-intensity tFUS is rarely used clinically for neuromodulating effects. The amplitudes and conduction velocities of evoked nerve potentials are enhanced or suppressed by low-intensity tFUS through force effect and cavitation effect, thereby modulating neuronal activity [76-78]. Additionally, tFUS can improve blood supply around brain lesion tissues [12].

The effect of tFUS depends on 5 main parameters: frequency, peak intensity, duration, pulse repetition frequency, and duty cycle. Deng et al [79] treated mice with low-intensity low-frequency (0.5 MHz) tFUS with Isppa of 39 mW/cm^2 for 10 min and found that it could reduce vasogenic edema after middle cerebral artery occlusion, as well as improve neural behavior and blood–brain barrier integrity. Wang et al [80] used tFUS with 120 mW/cm^2 and 1000 Hz for 10 min for 7 consecutive

Table 3. Summary of clinical studies on post-stroke patients using tACS.

Study	No.	Targeted lesion	Study design	Frequency	Peak current intensity	Location	Schedule	Follow-up	Outcomes
Gall et al, 2015 [68]	20 (20)	Unilateral occipital stroke	RCT	30 Hz	1.5 mA	Frontal pole midline point	20 min daily for 10 days	2 months	Visual field change positively
Wu et al, 2016 [66]	60 (30)	Subacute stroke	RCT	20 Hz	400 μA	bilateral mastoids	30 min daily for 3 weeks	N/A	NIHSS and the TCD parameters (MFV, PI) in MCAs, ACAs, and PCAs positive
Räty et al, 2021 [67]	9 (9)	Hemianopia after chronic stroke	RCT	5-15 Hz	1.5 mA	Bilateral frontal pole	30 min during days 1-5 and 40 min during days 6-10	2 months	No difference in the median detection accuracy

NIHSS – NIH Stroke Scale; TCD – Transcranial Doppler; MCA – middle cerebral artery; ACA – anterior cerebral artery; PCA – posterior cerebral artery; MFV – mean flow velocity; PI – pulsatility index.

Table 4. Summary of clinical studies on post-stroke patients using tFUS.

Study	No.	Targeted lesion	Study design	Intervention	Frequency	Intensity	Location	Schedule	Follow-up	Outcome
Zhou et al, 2017 [198]	80 (40)	Acute cerebral infarction	RCT	tFUS and acupoint application vs conventional	800 KHz	0.75 w/cm^2	Temporal window on the lesion side	30 d	N/A	Neurological function deficiency scale positive
Wang et al, 2020 [199]	45 (15)	Stroke	RCT	tFUS vs motor imagery vs conventional	800 KHz	1.2 W/cm^2	Temporal window on the lesion side	20 min for 4 weeks	N/A	FMA, MBI positive
Pu et al, 2021 [200]	114 (38)	Stroke with upper limb disorder	RCT	tFUS vs motor imagery vs conventional	800 KHz	1.2 W/cm^2	Temporal window on the lesion side	20 min for 4 weeks	N/A	FMA, MBI positive

FMA – Fugl-Meyer Assessment; MBI –Modified Barthel Index.

days in mice and found that tFUS can promote microglia polarization, reduce the inflammatory response, and improve neuron repair and remodeling, thus promoting post-ischemic stroke recovery. Nevertheless, as shown in **Table 4**, few studies have been done on tFUS for stroke, and more studies are needed.

Utilization of tVNS

Unlike other noninvasive techniques, tVNS does not stimulate the brain. It delivers electrical stimulation to the brain through the vagus nerve, causing changes in brain electrical activity and neurotransmitters, thus modulating the functional activity of neurons [81]. tVNS includes transcutaneous auricular VNS (taVNS) and transcutaneous cervical VNS (tcVNS) [82]. taVNS stimulates the auricular branch of the vagus nerve by surface current electricity, and the best anatomical site for stimulation is the auricular plate [83]. tcVNS represents the stimulation of the vagus nerve in the cervical pulse sheath, which is usually applied on the anterolateral surface of the vagus nerve and can activate it through the skin and other biological barriers [84].

The effect of tVNS on cortical excitability was first discovered by Capone et al [85], who found that paired-pulse stimulation selectively and significantly increased intracortical inhibition.

Table 5. Summary of clinical studies on post-stroke patients using tVNS.

Study	No.	Targeted lesion	Study design	Interv-ention	Frequency	Intensity	Schedule	Follow-up	Outcome
Capone et al, 2017 [91]	14 (7)	Chronic ischemic or hemorrhagic stroke	RCT	tVNS combined with robots vs sham tVNS with robots	20 Hz	Above the detection threshold and below the pain threshold	60 min for 10 d	N/A	FMA positive
Redgrave et al, 2018 [92]	13	More than 3 months postischemic stroke with residual upper limb dysfunction	CT	tVNS with concurrent upper limb repetitive task practice	25 Hz	Maximum tolerated intensity	>300 repetitions, 3 times a week for 6 weeks	N/A	FMA-UL positive
Baig et al, 2019 [93]	12	Ischemic stroke more than 3 months prior and moderate-severe upper limb weakness	CT	functional arm movement with taVNS	25 Hz	Maximally tolerated by the participant	300 repetitions for 6 weeks	N/A	FMA-UL for proprioception and light touch sensation positiive
Wu et al, 2020 [94]	21 (10)	Subacute Ischemic Stroke	RCT	taVNS vs sham	20 Hz	Individually selected by the patients according to tolerance	30 min for 15 consecutive days	4 weeks and 12 weeks	FMA-UL, WMFT, FIM, and Brunnstrom scores positive
Chang et al, 2021 [95]	36	Chronic, moderate-severe upper limb hemiparesis	CT	Shoulder/elbow robotic therapy aired with active taVNS or sham taVNS	30 Hz	Below the patient's reported pain threshold, with amplitudes ranging from 0.1 to 5.0 mA	1 h, 3×/week for 3 weeks	3 mo	FMA-UL, MRC, Wolf FAS, MTS positive
Li et al, 2022 [96]	60	Acute ischemic or hemorrhagic stroke	RCT	taVNS vs sham	20 Hz	According to the tolerance of each patient, and the average current intensity was 1.71±0.5 mA	20 min for 20 d	1 year	WMFT, FMA, HANDS, SIS positive

FMA-UL – Fugl-Meyer Assessment-Upper Limb; WMFT – Wolf motor function test; FIM – Functional Independence Measurement; MRC – Medical Research Council Motor Power Scale; Wolf FAS – Wolf Functional Ability Scale; MTS – Modified Tardieu Scale; HANDS – Hospital Anxiety and Depression Scale; SIS – the Stroke Impact Scale.

Moreover, another study [86] found that taVNS stimulation led to significant increases in neural activity in the right caudate nucleus, left prefrontal cortex, middle cingulate gyrus, and cerebellum. In addition, the mechanism of tVNS in stroke rehabilitation is also under investigation. The protective effect of tVNS on the blood–brain barrier has been proved in cerebral ischemia rats. It is achieved by reducing matrix metalloproteinase-mediated

tight junction protein destruction [87]. Subsequently, other animal experiments were carried out, showing that tVNS can reduce cortical infarct volume [88], inhibit neuroinflammation, and relieve nerve injury [89], thus improving neural function.

The stimulation parameters of tVNS have a great influence on clinical efficacy, as summarized in **Table 5**. The stimulus

current is usually set based on the subject's sensitivity or pain threshold. The amplitude of the stimulus varied over a wide range due to the varying tolerance of different participants to the stimulus. Studies have shown that the vagus nerve could receive remarkable irreversible damage when applying VNS greater than or equal to 50 Hz [90]. Recent clinical studies have used stimulation frequencies between 20 and 30 Hz [91-96].

Utilization of NIBS on Stroke Rehabilitation

Clinical Applications of NIBS in Motor Recovery After Stroke

Improvement in motor function for post-stroke patients with rTMS has been confirmed in many clinical trials. In 2012, LF-rTMS was demonstrated to improve upper limb mobility and strength in chronic stroke patients [97]. Sasaki et al [98] found that rTMS also improves rehabilitation of upper extremity motor function for apoplexy patients at an early stage, and HF-rTMS was better than LF-rTMS. A year later, they [99] discovered that stimulation with bilateral rTMS was more effective in restoring upper limb function than stimulation with unilateral high-frequency rTMS. Recently, Wang et al [100] discovered that motor function improvement of the upper limb by high- and low-frequency rTMS was influenced by the integrity of the corticospinal tract in patients, but high-quality experiments are still needed to confirm this. Simultaneously, rTMS has been shown to promote the rehabilitation of lower limb motor function in stroke patients [26,101]. It was interesting to find that patients with acute stroke sustained motor function recovery for 1 month and upper limb function improvement for 1 year after 10 days of rTMS [27]. The impact of rTMS on improving walking ability after stroke has been convincing. Stroke patient' gait and walking speed can be improved by rTMS [102]. rTMS can also improve hand function, including hand coordination, speed, grip strength, and fine movement, which has been shown in patients with acute, subacute, and chronic stroke [27,103-106].

tDCS is also commonly used in post-stroke patients with hemiplegia. Approximately 20 years ago, clinical trials of tDCS for motor rehabilitation after hemiplegia began [107,108]. The favorable effects of rTMS on recovery of upper extremity movement, flexibility, and hand grip strength in stroke patients have been demonstrated in acute, subacute, and chronic patients [11,109,110]. Moreover, some studies have found that the effect of bi-hemispheric tDCS is better than unilateral anodic tDCS in improving motor function [11,109]. For lower limb function and walking ability, rTMS also showed positive effects [111-113]. However, Aneksan [114] found that tDCS combined with task training was no more effective in improving gait and lower limb performance in patients with subacute stroke than training alone, but this was a small-sample study. Furthermore, rTMS can also help improve posture, exercise

planning, preparation, and execution in patients in the chronic phase, and more studies are needed in patients at different stages [45]. It is now generally accepted that earlier rehabilitation after a stroke is associated with better functional outcome. Bornheim [115] demonstrated that tDCS improved functional activity in patients with acute stroke and maintained it for up to 1 year. In addition, rTMS combined with tDCS stimulation could be a preferable rehabilitative strategy for motor recovery in stroke patients [116,117]. Also, tACS is beneficial for gait changes after a stroke. Gait-specific plasticity can be induced when tACS is synchronized with the gait period frequency [118].

tVNS has been applied for the recovery of upper extremity function for stroke patients. Redgrave [92] and Wu's [94] trial confirmed that tVNS is an effective and safe method for improvement of upper limb function in stroke, but the sample size was too small, requiring further confirmation by larger-sample studies. A recent study [96] demonstrated that taVNS was beneficial to both upper and lower extremity motor dysfunction in patients at the acute stage. The recent study mainly focused on upper limb function, and more high-quality studies are needed. Additionally, these trials have all used taVNS rather than tcVNS; therefore, it is hoped that taVNS will be used for post-stroke rehabilitation studies in the future.

Clinical Applications of NIBS in Sensory Recovery After Stroke

There were several studies of rTMS in the rehabilitation of sensory dysfunction after stroke. Liang [119] demonstrated that HF-rTMS can improve upper extremity sensory function involving pain threshold and two-point discrimination in stroke patients. Pundik [120] also found that rTMS can improve the two-point discrimination ability of chronic stroke patients, but has no effect on improvement of vibration sense and motor sense. At present, there is no published phased trial of rTMS for the treatment of sensory disorders after stroke, and the evaluation method is relatively subjective, so it is hoped that there will be further studies.

tDCS also helps improve sensory function in stroke patients. In 2014, a study [121] found that anodic tDCS reduced thermal pain and thermal pain thresholds in stroke patients, and increased cold and cold pain thresholds, suggesting that tDCS improved sensory recognition in stroke patients with central pain after stroke. Subsequently, Koo et al [122] demonstrated that tDCS improved tactile sense, pain sense, and cortical sensibility in patients with subacute stroke. Moreover, somatosensory performance was also improved by tDCS in acute patients and could be maintained for up to 1 year [115]. Further trials are needed to identify the effects of tDCS with diverse stimulation times, stimulation methods, and longer follow-up periods.

tVNS has been demonstrated to improve stroke patients' proprioception. Baig et al [93] treated ischemic stroke patients with taVNS for 6 weeks, and their proprioception and light touch improved after treatment. Furthermore, another study [96] has confirmed the taVNS has long-term effects on sensory dysfunction in acute stroke patients, but the measurement tools were not accurate, and specific sensory improvement needs to be studied.

Clinical Application of NIBS to Recovery From Post-Stroke Aphasia

In 2011, the first randomized and sham-stimulation controlled trial of rTMS in stroke patients at the subacute stage was reported by Weiduschat et al [123]. They found that rTMS is an effective, safe, and viable complementary treatment for post-stroke aphasia. LF-rTMS has been shown to improve spontaneous speech, naming, auditory comprehension, and functional communication in stroke patients with aphasia, especially subacute patients, for at least 3 months [124-127]. Hu [128] found that, compared with HF-rTMS, LF-rTMS performed better in improving auditory comprehension, spontaneous speech, and aphasia quotients (AQ) in stroke patients. The therapeutic effect of rTMS may be related to the stimulus site. After applying LF-rTMS in the right posterior superior temporal gyrus, auditory comprehension and repetition improved significantly, while inhibition in the posterior inferior frontal gyrus contributed to a significant enhancement of spontaneous speech and repetition [129]. Recently, a randomized sham-controlled blinded study [32] first found that subacute aphasia patients received a better effect by 1 Hz subthreshold rTMS over the pars triangularis of the right inferior frontal gyrus compared with patients in the chronic phase. Now, more research is focusing on the effects of rTMS on functional communication, with the ultimate goal of restoring communication in everyday life. The effectiveness of tDCS in improving the accuracy and speed of image naming in people who lose their speech after a stroke, especially in the chronic phase, has been confirmed by several experiments [130-134]. Branscheidt [135] demonstrated that the overall accuracy in a lexical decision task was improved when the motor cortex of the dominant hemisphere received the anodal stimulation. Moreover, a randomized sham-controlled study [136] showed that applying anodal tDCS over the left M1 can recover patients' speech function, and can also excite and recruit more areas in the motor speech network. However, some recent studies [137,138] have shown that tDCS does not improve the disturbance of speech in post-stroke patients with aphasia and may not be as effective as adjuvant treatment for post-stroke aphasia.

Although tDCS and rTMS have been shown to increase the chances of reasonable recovery of language after strokes in clinical trials, these treatments locally activate glutamate and GABA neurons and interfere with circuits that regulate motor function [139], whereas tVNS only increases neuromodulation and does not interfere with ongoing nerve impulses [140]. There are no clinical studies on tVNS in treating post-stroke dysphagia, but tVNS has potential as a means to promote the recovery of speech impairment after stroke [141].

Clinical Applications of NIBS in the Rehabilitation of Dysphagia After Stroke

In 2013, Park [142] observed a reduction in the prevalence of aspiration and pharyngeal residuals in stroke patients after treatment with 5 Hz rTMS. Studies using rTMS in dysphagia after acute and chronic stroke have been carried out. Most studies have reported beneficial effects [143-145], but some trials have found that rTMS also improves dysphagia [146,147]. The site of stimulation affects bilateral or contralateral stimulation, but not ipsilateral stimulation [148]. Compared with 10 Hz, 5 Hz, and 1 Hz, Du [145] found that swallowing function improved after treatment with 10 Hz rTMS. In general, rTMS appears to be a promising therapy for post-stroke dysphagia, although the standard stimulus parameters still need to be investigated.

Many trials have proven that tDCS enhances cortical input, supports swallowing network reorganization, and may be beneficial for dysphagia recovery [149-153]. Suntrup-Krueger et al [153] used clinical assessment and the validated Fiberoptic Endoscopic Dysphagia Severity Scale (FEDSS) to assess deglutition function, and found greater improvement in FEDSS with each hour of treatment starting earlier. A recent study [154] focused on patients' diets and found that dietary intake was improved but the risk of aspiration was not reduced by tDCS in patients at the early stage. This study's sample size was small, and large-scale trials are needed to validate it.

Clinical Applications of NIBS in the Rehabilitation of PSD

rTMS has been widely used as a complementary therapy for depression, and research on its use in PSD is also ongoing. It has been shown that the use of rTMS over the left DLPFC can alleviate PSD in the chronic phase [155]. A meta-analysis [156] also suggested an active effect of rTMS on PSD, but heterogeneity and potential biases in such studies should be carefully examined. Recent studies [29,157] have demonstrated the efficacy of HF-rTMS for PSD and found changes in functional brain connectivity in patients before and after treatment.

Studies on tDCS to treat depression after stroke are still in the preliminary stage. Valiengo [158] found that 2mA of tDCS applied to patients' left and right DLPFC can effectively improve depressive symptoms. Bornheim [115] also found that tDCS improved PSD and the effect lasted for 1 year. It seems that

tDCS is a safe and effective therapy for PSD, but trials with larger samples, longer follow-ups, and more accurate outcome measures are needed.

Currently, there are no clinical trials of tVNS in the treatment of PSD, but tVNS is commonly used in the treatment of depression, which can cause some changes in brain functional connectivity in PSD patients and significantly relieve depressive symptoms [159]. In addition, tVNS is convenient to use and conducive to clinical use. Therefore, tVNS can be tried as a treatment for PSD.

Clinical Application of NIBS to Rehabilitation of Post-Stroke Unilateral Neglect

Many experiments[25,160,161] have found that 1 Hz repetitive rTMS of the unaffected hemispheric parietal cortex improves unilateral neglect after stroke. Yang [30] and Zhang [162] combined rTMS with sensory cues and found that the combination was more effective for unilateral neglect after stroke than rTMS alone. However, the effectiveness of 1 Hz rTMS applied in the angular gyrus in combination with visual scanning training in patients with unilateral spatial neglect (USN) in the subacute phase has not been determined [163].

In 2008, Ko [164] first reported that the polarization of the parietal cortex direct current could improve the visual scanning in USN patients. Subsequently, many researchers [165,166] have found that the excitatory effect of tDCS anode on the right posterior parietal cortex and the inhibitory effect of tDCS cathode on the opposite improved unilateral neglect symptoms, while bilateral tDCS is more effective than unilateral stimulation. In severely impaired patients in the acute phase, tDCS combined with optokinetic drift relieved egocentric neglect but not allocentric neglect, Turgut et al found [167]. Recent studies [168] focused on the feasibility of a trial in patients and found it was poor, as too many patients had to be excluded due to serious complications. Thus, the basis for recruitment, the criteria of eligibility, and the parameters and location of interventions should be carefully considered in future studies on using tDCS in unilateral neglect.

Clinical Applications of NIBS in Treating Post-Stroke Cognitive Impairment (PSCI)

Only a few small-scale studies have explored the impact of rTMS on cognitive function in stroke patients. In 2010, Kim et al [169] performed rTMS at 10 Hz and 1 Hz in the dorsolateral prefrontal region for 2 weeks and found no significant improvement in cognitive function. Five years later, Lu et al [170] found that 4 weeks of rTMS at 1 Hz enhanced cognitive function and memory function after stroke. Subsequently, many studies [171,172] have found that HF-rTMS can also improve overall cognition, attention, and memory function after stroke, but there is currently a lack of large-scale, long-term follow-up trials investigating the impact of rTMS on cognitive function after stroke. Recently, Li et al [173] discovered that serum tri-iodothyronine, free triiodothyronine, and thyroid-stimulating hormone levels of stroke patients were positively correlated with MoCA score, and rTMS increased these thyroid hormone levels to enhance patients' cognitive function.

tDCS also contributes to the recovery of cognitive impairment. About 2 decades ago, studies found that anodic tDCS acting on the dorsal prefrontal lobe improved working memory [174] and attention [175,176] in patients. Moreover, Shaker et al [177] demonstrated that tDCS is a safe and effective neurorehabilitation model that improves cognitive function in several areas, including attention and attention, graphic memory, logical reasoning, and reactive behavior. Recently, a study discovered that tDCS combined with cognitive training significantly enhanced motivation, valuation, and decision-making abilities in stroke patients.

There are several studies on cognitive impairment after stroke with tFUS. Wang and colleagues[178] found that transcranial ultrasound together with routine cognitive training significantly improved cognitive function after stroke. Currently, there are no clinical trials of tVNS in the treatment of PSCI, but animal experiments [179] have found that neuronal stimulation can improve spatial and fear memory in rats with middle cerebral artery occlusion, and the clinical efficacy needs to be further explored.

Safety of NIBS

rTMS is well tolerated in clinical use and is a relatively safe method, but can cause adverse effects such as seizures, headache, neck pain, and transient hearing abnormalities. In Kakuda's study [180], 1725 patients were stimulated with rTMS, and a total of 22 patients reported temporary but not severe adverse effects, including mild dizziness, mild headache, and discomfort at the site of the stimulation. Seizure is the most serious adverse effect of rTMS and is more common with the use of HF-rTMS. Although many patients are receiving rTMS in clinical trials, few cases have been reported, so it appears the risk of rTMS inducing seizure is relatively low [181]. Several factors may increase the risk of rTMS-induced seizures, such as sleep deprivation, stress, depression, and excessive alcohol consumption [182]. Care should be taken to avoid these factors in clinical application, and preparation for the possibility of seizures is necessary. Headache and regional pain at the site of stimulation are common adverse effects of rTMS. The incidence of these adverse effects may depend on the intensity, location, and frequency of stimulation. Therefore, clinical use of rTMS should follow the safety recommendations

of relevant guidelines [183] and exclude patients with contra-indications. More high-quality evidence is needed to explore the relationship between stimulus parameters and adverse reactions. In addition, the localization of rTMS is relatively inaccurate in clinical use, and inaccurate position and direction of the coil may reduce the response rate of patients while affecting irrelevant brain regions [184], so neuroimaging such as functional magnetic resonance imaging can be applied to help localization [185].

Compared to rTMS, tDCS has a better clinical safety profile, with no serious adverse effects [186]. However, there are still minor adverse reactions in the treatment process, such as skin redness, slight tingling, dizziness, and fatigue, which are safe, short-lived, and can be tolerated by most patients. The efficacy and safety of tDCS are dose-dependent, with higher current intensities providing better efficacy and potentially more brain damage. Currently, a single dose of 4 mA tDCS for 30 min is considered tolerable and safe in stroke subjects in clinical studies [187], and tDCS with current intensity ≤ 2 mA is mostly used for treatment [188]. Moreover, the charge density is more comprehensive than the current density in judging the safety of tDCS, since the charge density parameter takes into account the duration of the stimulus, such as 1 mA for 10 min, 2 mA for 5 min, and 10 mA for 1 min which have similar charges. Therefore, during the clinical application of tDCS, the relationship between dose and efficacy should be considered and the most appropriate parameters for the patient are effective and safe.

tFUS is used for neuromodulation in humans, without any reports of serious related symptoms; moderate and mild symptoms may occur, including neck pain, inattention, muscle twitching, and anxiety [189]. A study [190] found that symptoms generally appeared after the stimulation ended, none of these symptoms persisted after 1 month of follow-up, and no new symptoms were reported. Animal studies [191] have found microbleeds in the primary visual cortex of sheep after 600 treatments with tFUS of 6.6 W/cm^2 Isppa, but the Ispta value of 3.3 W/cm2 exceeds the physical therapy US limit of 3 W/cm^2. FDA guidelines [192] define safety thresholds for an ultrasound for head ultrasound diagnosis and neural regulation in adults that are Isspa ≤ 190 W/cm^2, Ispta ≤ 94 mW/cm^2, together with mechanical index ≤ 1.9, which need to be appropriately evaluated in future studies to select the safety parameters of tFUS for neurological rehabilitation.

So far, the clinical use of tVNS has been relatively safe and well tolerated. The most common adverse effects are local skin irritation, headache, and dizziness, but these are short-lived and may resolve during treatment [193,194]. Palpitations, arrhythmias, hypotension, and bradycardia were also reported in a small number of patients, but their association with nVNS has yet to be examined [195,196].

Discussion

The current clinical status [2,3] showed that stroke is extremely harmful, the incidence is increasing, and the motor, sensory, speech, swallowing, and other functions of survivors are seriously affected. Therefore, how to improve the functions of stroke survivors is the key and difficult point in clinical practice. Our extensive literature review found that the application of NIBS in treating stroke is an important research focus. The recent literature shows that NIBS, including rTMS, tDCS, tACS, tFUS, and tVNS, can improve functions in stroke patients. In particular, in terms of motor function, the studies found that function of patients with stroke can be significantly improved with rTMS [102] or tDCS [11] combined with traditional rehabilitation treatment. Additionally, tVNS, which sends electrical stimulation to the brain via the vagus nerve, has also been verified to improve motor and sensory functions in stroke patients [93]. However, there have been few trials on the use of tACS and tFUS in stroke rehabilitation. One study [67] has shown that tACS has no benefit for curing hemianopia after stroke, but tACS and tFUS have been used to treat the dysfunction caused by other clinical diseases, showing their potential in stroke rehabilitation in the future. Some studies [12,41] have found that NIBS can improve the vascular structure, morphology, and cerebral blood flow in stroke patients, which also indicates that NIBS is beneficial for stroke patients. The present article reviewed the status of research of the mechanism of action, therapeutic parameters, efficacy, and safety of NIBS in patients after stroke, and discussed its future development trend, to support the clinical application of NIBS in stroke rehabilitation. We look forward to publication of more high-quality evidence to verify the role of NIBS in stroke rehabilitation in the future.

Conclusions

NIBS has been shown to effectively improve motor, sensory, speech, swallowing, cognitive impairment, and depression after stroke. However, due to the lack of standardized stimulus protocols and single-use efficacy validation, the potential clinical utility of NIBS needs to be confirmed by higher-quality evidence-based medicine results.

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