Physical Therapy and Rehabilitation
ISSN 2055-2386 | Volume 9 | Article 1

HOAJ
Herbert Open Access Journals

Review Open Access

Non-Invasive Brain Stimulation in Stroke- Our Experience and an Overview

Ashu Bhasin[1], Neha Kuthiala[2], M V Padma Srivastava[3] and Senthil S Kumaran[4*]

*Correspondence: senthilssk@yahoo.com

[1]Consultant (Medical), Department of Neurology, AIIMS, New Delhi, India.
[2]Research officer, Department of Neurology,AIIMS, New Delhi, India.
[3]Head, Department of Neurology, AIIMS, New Delhi, India.
[4]Professor, Department of NMR & MRI facility, AIIMS, New Delhi, India.

Abstract

Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have great therapeutic potential in diagnostic and interventional neuroscience, neurophysiology and psychiatry. These have emerged as a boon for stroke recovery in the last decade. TMS allows neurostimulation and neuromodulation, while tDCS purely converges in neuromodulation. This review on non invasive brain stimulation (NIBS) provides a comprehensive summary of the current evidence in stroke upper motor recovery with most robust reviews, recent trials included at clinicaltrials.gov, pubmed, CINAHL and other search engines. We also expand this review with our experience of both the interventional modalities for post stroke arm and hand function recovery. Our results show that NIBS works on neurophysiological principles of learning & plasticity and aids in motor performance when applied in different stages of stroke recovery.

Keywords: Non invasive stimulation, stroke, neural rehabilitation, upper limb recovery

Introduction

The amalgamation of bioelectrical and engineering domains with medical sciences has led to the development of newer technologies like noninvasive brain stimulation (NIBS). This has proved to be a valuable tool for interventional neurophysiology applications which modulates brain activity to induce controlled manipulations in function and behavior [1]. Brain stimulation techniques have a theoretical appeal of being able to specifically and selectively enhance adaptive patterns of CNS activity, suppress mal adaptive patterns and restore equilibrium in imbalanced neural networks [2,3].

There is surmounting evidence for the efficacy of noninvasive brain stimulation in various neurological conditions. In this report we present a comprehensive review of non-invasive brain stimulation techniques like transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) in Stroke [4,5]. TMS is a neurostimulation and neuromodulation device, whereas tDCS is a purely neuromodulatory intervention [6,7].

NIBS and neural plasticity after stroke

Neuroplasticity refers to the ability of the nervous system to change its structure and function, adapting to environmental changes to recover after any brain lesion [8,9]. The most commonest principles are "recruitment" and "compensation" of other brain areas than the injured one. The stimulation through TMS or tDCS induces behavioral changes and the response of the brain to such behavioral changes is augmented and captured by these modalities [10,11]. NIBS for stroke patients works on two theoretical models as suggested by reviewers: (i) an interhemispheric inhibition of human motor cortices on one another; and (ii) the transcallosal inhibitory effect on the affected motor cortex because of the above said phenomenon [12,13]. Therefore, the approach for applying tDCS and or TMS generally has been to either up-regulate the lesional hemisphere with excitatory anodal stimulation, down-regulate the contralesional hemisphere with inhibitory cathodal tDCS stimulation, or use excitatory TMS on lesional hemisphere or exploit an inhibitory effect on contralesional hemisphere [14,15] (Figures 1 and 2).

In the present review we focus on these two interventions; an overview of the modalities, past reviews, current trials and our experience in stroke.

Methods

Inclusion criteria are as follows

- Research trials on non-transcranial magnetic stimulation, transcranial direct current stimulation for motor upper limb impairments after stroke.
- Rehabilitation in the acute, sub-acute, and chronic phases after stroke.
- Randomised controlled trials, case reports, case controlled studies were included.
- Articles published from January 2015 till October 2020.

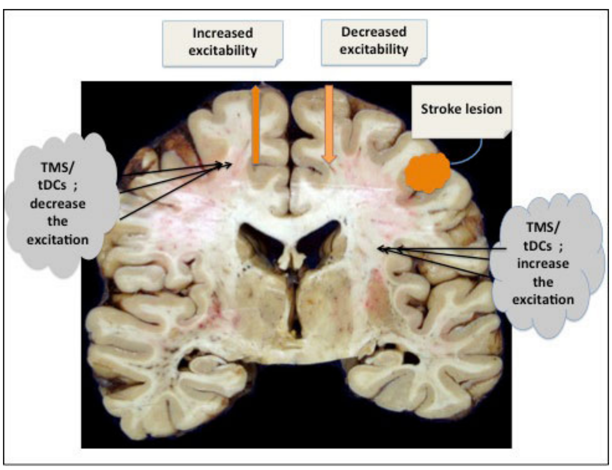

Figure 1. Excitatory and inhibitory effects of non invasive brain stimulation (NIBS).

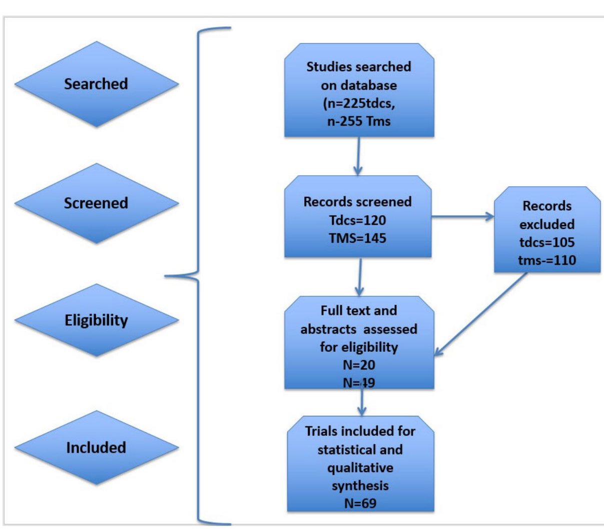

Figure 2. PRISMA selection of research articles.

Exclusion criteria are as follows

- Studies written in languages other than English.
- Reports studying the effects of NIBS on lower limb, gait and postural rehabilitation.

Search Strategy

This review was conducted using PRISMA guidelines (Figure 2). An electronic search was performed using PubMed, Web of Science, CINAHL. The search strategy includes keywords combined with following words: TMS, stroke, NIBS, rehabilitation, functional recovery. The selection strategy of the studies is shown in the PRISMA flow chart.

Review Process

The studies were screened by two authors based on their titles and abstracts. All of the full articles were then assessed in order to check the fulfillment of the inclusion criteria. In case of a disagreement between the selection, the decision was made by the corresponding author.

Data Extraction

After the selection of studies, the data were extracted for information on the title, inclusion and exclusion criteria, type of intervention, sample size, study methodology, primary and secondary outcomes, study limitations, feasibility, and adherence. The data collected were mainly divided on the basis of application in stroke rehabilitation, modes of intervention delivery, and types of control and outcome assessment.

Transcranial magnetic stimulation (TMS)

Device and design

Transcranial magnetic stimulation (TMS) is a non-invasive technique of stimulating the cortex using a wired coil placed over the scalp to generate a short-lasting and localised magnetic field [16,17]. The pulsed magnetic field enters the brain and creates an electrical current that flows through neurons, inducing neuronal depolarization. rTMS is defined as repetition of TMS pulses; high-frequency rTMS increases cortical excitability, whereas low-frequency rTMS suppresses cortical excitability (Figure 3). Another module is theta burst stimulation (TBS) which consists of short bursts of 3 stimuli at 50 Hz, repeating at 5 Hz [18]. The continuous pattern (cTBS; 200 bursts, 600 stimuli, 40 s) suppresses cortical excitability and was delivered to the contralesional hemisphere; the intermittent pattern (iTBS; 20 trains of 10 bursts with 8-s intervals, 600 stimuli, 200 s) enhances excitability and was delivered to the ipsilesional hemisphere [19].

It has been reported that high-frequency rTMS resulted in a significantly increase in the MEP amplitude than the sham rTMS ($p<0.01$), and the plastic change was positively associated with an enhanced motor performance accuracy ($p<0.05$). It was concluded that high-frequency rTMS of the affected motor cortex can facilitate practice-dependent plasticity and improve the motor learning performance in chronic strokes [20].

doi: 10.7243/2055-2386-9-1

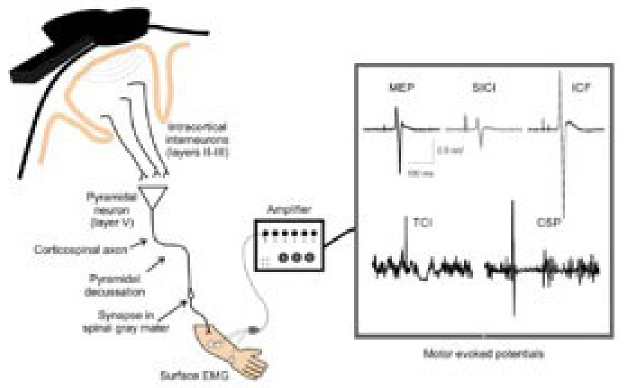

Figure 3. Taken from Auriat et al 2015; Frontiers in Neurology; A schematic of TMS evoked measures of single and paired pulsed corticospinal excitability.

Cellular data show that rTMS modulates excitability of both γ-aminobutyric acid (GABA) and glutamatergic neurons. Repeated 1-Hz stimulation particularly increased gene expression associated with synaptic plasticity and GABA-producing enzymes, as well as GABAergic neurotransmission on the system level [21].

TMS & stroke recovery

A review by Xiang et al 2019 evaluated the effects of repetitive transcranial magnetic stimulation (rTMS) on limb movement recovery and cortex excitability, to explore the optimal parameters of rTMS and suitable stroke population. They found 42 eligible studies involving 1168 stroke patients indicated that rTMS had positive effects on limb motor recovery (SMD=0.50, p<0.00001) and activities of daily living (SMD = 0.82, P<0.00001), and motor-evoked potentials [22]. Another review quoted that rTMS is favorable in acute stroke than sub acute strokes [23]. One review commented on 34 studies and found that five-session rTMS treatment could best improve stroke-induced upper limb function and dyskinesia acutely and in a long-lasting manner [24].

One of our double blind, randomized controlled research trial investigated the role of low-frequency rTMS (10 Hz, 750 pulses with 110%RMT) along with conventional physiotherapy on 60 chronic ischemic stroke patients from 3 to 36 months of index event with atleast 10° of wrist extension & thumb abduction with brunnstorm stage 2-4. Patients were randomized equally to CIMT & rTMS with CIMT groups and were assessed with clinical scales and fMRI at baseline, 21st & 90th day. We observed a significant change in FM showed statistically significant improvement in group B as compared to group A at 3 weeks (95%CI: -12.4 to -9.3, p=0.003) and 3months (95%CI : 7.4 to 4.2, p=0.01. There was an increase in the BOLD cluster activation in rTMS group as compared to the one who received CIMT alone [25].

Our experience with first ever ischemic stroke was carried out with low frequency repetitive TMS stimulation in a double-blind, parallel group, randomized controlled trial. The primary efficacy outcome measures were a change in modified Barthel Index (mBI), Fugl-Meyer score, Hamilton depression Scale, modified Rankin score measured at 90±7 days post recruitment. Patients were randomized after a run-in period of 75±7 days into real rTMS (n=47) and sham rTMS (n=49) groups. Total 10 sessions of low-frequency rTMS on contralesional premotor cortex was administered along with conventional physiotherapy were administered for 2 weeks for 45-50 minutes. Modified intention to treat analysis showed a significant increase in the mBI score in real rTMS group (4.96±4.06) versus sham rTMS group (2.65±3.25). There was no significant difference in proportion of patients with mBI>90 (55% vs 59%; p=0.86) at 3 months between the groups. 1-Hz low-frequency rTMS on contralesional premotor cortex along with conventional physical therapy resulted in significant change in mBI score [26,27].

Transcranial direct current stimulation (tDCS)

Device and design

This device delivers constant direct current (e.g.,0–4mA) while constantly monitoring the resistance in the system. Saline soaked electrodes are applied and secured onto the scalp over desired areas like the left or right precentral gyrus region (corresponding to C3 or C4 of the international 10–20 EEG system) (Figure 4). The relaying currents are put across the scalp and pass through the underlying brain tissue. The direction of the current flow determines the effects on the underlying tissue [28]. With an active electrode over C3 or C4, a reference electrode (e.g. supra-orbital region) is kept distant to complete the circuit. Two modes of TDCS have been used: anodal stimulation which increases in excitability of the lesional hemisphere or cathodal stimulation which decreases the excitability of the contralesional hemisphere. The excitability under anode is increased and when the current flow is reversed, the excitability of the brain tissue under this electrode is decreased [29].

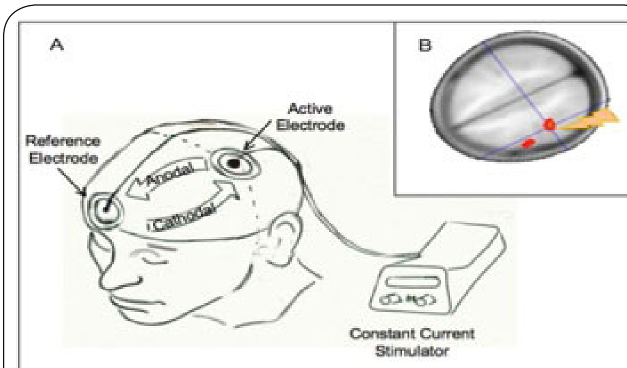

Figure 4. Taken from Schlaug et al; Arch Neurol 2008. tDCS device and its applications.

doi: 10.7243/2055-2386-9-1

The advantages of tDCS over other NIBS methods is its portability, easy usage, electrode size which allows a large neural network for stimulation, a sham mode and simultaneous rehabilitation being administered to subjects. Moreover it is less risky than direct cortical or epidural stimulation and can be performed on an outpatient basis, with optimal montage of electrodes [30,31]. GABAergic and dopaminergic modulation of tDCS-induced effects were reported by Nitsche et al through long-term potentiation (LTP) and long term depression (LTD) [21].

Transcranial direct current stimulation & ischemic stroke

tDCS has a large data bank with most of the studies depicting positive results after stroke [32,33]. These studies mostly applied a single or multiple sessions of tDCS and evaluated the effects comparing performance in pre and post intervention batteries of motor assessments. We came across more than hundred trials of tDCS for motor, cognitive, balance and gait disorders after stroke. In Tables 1 and 2 we have combined the study designs in the last 5 years with special mention to arm recovery. tDCS could be an effective approach to

Table 1. Clinical studies of Transcranial Magnetic Stimulation (TMS) in stroke.

Study Title	Interventions/Age	Study Design	Outcome Measures
Multifocal Brain **Magnetic Stimulation** in Chronic Ischemic **Stroke** NCT0281707 (2019-2020)	r**TMS**; 18 Years and older	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor)	Percent of activated voxels in the cortical areas Fugl Meyer motor; ARAT (Action Research Arm Test)
The Effect Of TMS In Patients With **Stroke** NCT04562415 2019-2020	Device: Active & sham Theta Burst TMS 18 Years to 80 Years	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Outcomes Assessor)	Upper Extremity Fugl-Meyer Motor Function Scale Modified Ashworth Scale Functional Independence Measure
Use of Deep TMS After **Stroke**	Device: Deep TMS (**Transcranial magnetic stimulation**) Device: Brainsway Deep TMS 18 Years to 85 Years	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	modified Rankin score (mRS). Safety (mortality, symptomatic ICH, asymptomatic ICH, hematological, cardiac, liver etc) NIH stroke scale score at discharge
Effects of Repetitive TMS Combined With Sensory Cueing on Unilateral Neglect in Subacute Patients With Right Hemispheric **Stroke** NCT02645344 (2015-2018)	Device Repetitive **Transcranial Magnetic Stimulation** (rTMS) Behavioral: Sensory Cueing (SC) 18 Years and older	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Outcomes Assessor)	Behavior Inattention Test (BIT) Catherine Bergego Scale (CBS) Fugl-Meyer Assessment (FMA)
Cortical Excitability Sequential Changes in Response to **TMS** Post **Stroke** NCT03845595	Device: (LF-rTMS) group Other: Control group 50 Years to 65 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Participant)	cortical excitability mean values Upper limb motor performance
rTMS and Conventional Physical Therapy After **Stroke** NCT01875536	Device: rTMS Behavioral: conventional physical therapy 30 Years to 75 Years	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor)	Modified Ashworth scale; Hoffmann reflex of the median nerve Fugl-Meyer assessment; cortical excitability via single **transcranial magnetic stimulation**
Repetitive **TMS** Use in Acute **Stroke** NCT01922986	Device: active & sham rTMS Behavioral: conventional stroke therapy 18 Years and older	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Outcomes Assessor)	Jebsen Taylor Hand Function Finger Tracking; Motricity Index
Adjunct Low Frequency r**TMS** With Physiotherapy Enhance Upper Extremity Function Restoration NCT02490371	Device: Low frequency rTMS Behavioral: structured physiotherapy upper limb training up to 85 Years	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Outcome Assessor	Cortical Excitability From Motor Evoked Potential at 120% Resting MotorThreshold Fugl-Meyer Assessment; Grip Strength

doi: 10.7243/2055-2386-9-1

Continuation of Table 1.

Study Title	Interventions/Age	Study Design	Outcome Measures
Contrastim **Stroke** Trial NCT01049802 (2013)	Device: rTMS 18 Years to 90 years	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Outcomes Assessor)	Upper Extremity Fugl-Meyer Score Action Research Arm Test Stroke Impact Scale
Trans Cranial Brain **Stimulation** for **Stroke** Rehabilitation NCT03122821 (2018-2019)	Other: **TMS**+Mental Imagery 40 Years to 80 years	Allocation: Randomized Intervention Model: Factorial Assignment Masking: Quadruple (Participant, Care Provider)	Action arm inventory for stroke Quality of movement
Repetitive rTMS Treatment of Post-**Stroke** Spasticity NCT02268461 (2014-2016)	Device: real and sham rTMS 18 Years and older	Allocation: Randomized Intervention Model: Crossover Assignment Masking: Triple (Participant, Care Provider, Outcomes Assessor)	Ashworth Scale score Pre-Post-treatment) Change in Baseline Active Range of Motion
A Brain Centered Neuroengineering Approach for Motor Recovery After **Stroke**: Combined rTMS and BCI Training NCT02132520	Device: rTMS Behavioral: BCI Training 18 Years to 70 years	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Participant)	Changes in Cortical Excitability Box and Block Test Finger Tracking Test
Effects of rTMS Based on Brain Activation During Language Performance in **Stroke** Patients With Non-fluent Aphasia NCT02556385	Device: High frequency rTMS Device: Low frequency rTMS 18 Years to 80 Years	Allocation: Non-Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Care Provider	BNT (Boston naming test; Western aphasia battery) Laterality index (LI)
Mechanisms of Arm Recovery in **Stroke** Patients With Hand Paralysis NCT03067818 (2017-2019)	Procedure: Control **Transcranial Magnetic Stimulation** 18 Years to 85 Years	Allocation: Randomized Intervention Model: Crossover Assignment Masking: Single (Outcomes Assessor)	Change in movement; maximum reaching distance hand path kinematics
Modulating Interaction of Motor Learning Networks in Rehabilitation of **Stroke** NCT03086551 (2016-2019)	Device: Active & sham continuous theta burst **stimulation** (cTBS) 50 Years to 75 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Crossover Assignment Masking: Double (Participant, Outcomes Assessor)	Change From Baseline in Time to Complete the Jebsen-Taylor Hand Function Test Immediately Follow an Individual Bout of Non-invasive Brain **Stimulation** (e.g. Within Session)
NIBS and Dual-task Walking After **Stroke** NCT03442868	Device: high frequency rTMS 18 Years and older (Adult, Older Adult)	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label)	change in gait speed;step lengths change in single support times; counting task performance
Combined Neural and Behavioral Therapies to Enhance **Stroke** Recovery NCT00929656	Procedure: Real & sham rTMS Unimanual paretic UE Training 18 Years to 80 years	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Outcomes Assessor)	Wolf Motor Function Test Change Fugl-Meyer Motor Assessment Grip Strength
The Combining rTMS With Visual Feedback Training for Patients With **Stroke** NCT03689491	Behavioral: rTMS Behavioral: visual feedback training 20 Years to 80 Years	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Outcomes Assessor)	Change of Motor evoked potential Chang of Motor Assessment Score Chang of Berg Balance Test
Using **Transcranial** Direct Current **Stimulation** (tDCS) to Enhance the Benefit of Movement Training in Stoke Patients NCT00783913	Other: Visumotor Upper Extremity Training Other: Anodal/Sham tDCS 18 Years to 85 Years	Allocation: Randomized Intervention Model: Factorial Assignment Masking: Double Primary Purpose: Treatment	accuracy (difference between the straight line connecting the origin and the target and the line followed by the subject) during reaching. FM score

Continuation of Table 1.

Study Title	Interventions/Age	Study Design	Outcome Measures
Brain **Stimulation** and Robotics in Chronic **Stroke** Motor Recovery NCT03562663	Device: **Transcranial** direct current **stimulation** Device: Upper extremity robotics 18 Years and older (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Care Provider, Outcomes Assessor)	Upper Limb Fugl Meyer Wolf Motor Function Test Barthel Index Stroke Impact Scale
Use of **Transcranial** Direct Current **Stimulation** (tDCS) Coupled With Constraint Induced Movement Therapy in **Stroke** Patient NCT01143649	Device: tDCS & tACS constraint induced movement therapy (CIMT) 18 Years to 90 Years	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Outcomes Assessor)	Jebsen Taylor Hand Function Test Cortical Excitability Cortical Oscillations - EEG
Novel Brain **Stimulation** Therapies in **Stroke** Guided Expressions of Plasticity NCT03020433	Device: rTMS Contralesional and ipsilesonal M1 & PMC 21 Years and	Allocation: Randomized Intervention Model: Crossover Assignment Masking: Single (Participant)	Aim 1: Change in time (seconds) to perform functional reaching Aim 2:Change in plasticity evoked with rTMS.

Table 2. Clinical studies of Transcranial direct current stimulation (tDCS) in stroke.

Study Title	Age/Interventions	Study Design	Outcome Measures
Trans Cranial Brain **Stimulation** for **Stroke** Rehabilitation NCT03122821 (2016-2018)	• Other: 3 GROUPS **Transcranial direct stimulation**+Mental Imagery • Other: **Transcranial** magnetic **stimulation** • Chronic; 40 Years to 80 Years (Adult, Older Adult)	• Allocation: Randomized • Intervention Model: Factorial Assignment • Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	• Action arm inventory for stroke • Quality of movement
Effect of Home Based **Transcranial Direct** Current **Stimulation** (tDCS) With Exercise on Upper and Lower Limb Motor Functions in Chronic **Stroke** NCT04226417 (2019-2020)	Device: **Transcranial direct** current **stimulation** 18 Years to 75 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Factorial Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor)	Fugl-Meyer Assessment in upper & lower limbs Wolf Motor Function Test Five-times Sit to Stand Test
Brain **Stimulation** and Robotics in Chronic **Stroke** Motor Recovery NCT03562663 (2016-2017)	Device: **Transcranial direct** current **stimulation** Device: Upper extremity robotics Chronic; 18 Years and older (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Care Provider, Outcomes Assessor)	Fugl Meyer;Wolf Motor Function Test Barthel Index; Stroke Impact Scale
Safety of **Transcranial Direct** Current **Stimulation** in the Subacute Phase After **Stroke** NCT02455427 (2015-2018)	Device: Active tDCS Other: Physical Therapy Device: Sham tDCS 18 Years and older (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Outcomes Assessor)	Safety by frequency of adverse events Modified Rankin Scale; NIH Stroke Scale
Effects of Dual-**transcranial Direct** Current **Stimulation** During Physical Therapy in Sub-acute **Stroke** NCT04051671	Device: **Transcranial direct** current **stimulation** 18 Years to 75 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Crossover Assignment Masking: Double (Participant, Investigator)	Five-Times-Sit-To-Stand test (FTSST) Timed Up & Go test (TUG)

doi: 10.7243/2055-2386-9-1

Continuation of Table 2.

Study Title	Age/Interventions	Study Design	Outcome Measures
Use of **Transcranial Direct** Current **Stimulation** (tDCS) Coupled With Constraint Induced Movement Therapy in **Stroke** Patient NCT01143649	Device: **transcranial direct** current **stimulation** (tDCS) Procedure: CIMT Device: **transcranial** alternating current **stimulation** (tACS) 18 Years to 90 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Outcomes Assessor)	Jebsen Taylor Hand Function Test Cortical Excitability Cortical Oscillations - EEG
Effects of Bihemispheric **Transcranial Direct** Current **Stimulation** on Motor Function in **Stroke** Patients NCT03839316	Device: tDCS Device: sham tDCS 18 Years to 75 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Outcomes Assessor)	Change in upper extremity impairment Change in functionality Change in motor activity
Optimizing **Transcranial Direct** Current **Stimulation** for Motor Recovery From Hemiparesis NCT03124147	Device: Neuroconn Eldith stimulator by Magstim 18 Years and older (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor)	Change in Fugl Meyer Assessment Change in Action Research Arm Test Change in Stroke Impact Scale
Combined **Transcranial Direct** Current **Stimulation** and Motor Imagery-based Robotic Arm Training for **Stroke** Rehabilitation NCT01897025	Device: real-tDCS with MI-BCI 21 Years to 70 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Outcomes Assessor)	Fugl-Meyer Assessment; RMT Affected M1 Motor Cortex; Grip Strength
Randomized Trial of **Transcranial** Theta-burst **Stimulation** and **Transcranial Direct** Current **Stimulation** NCT02031107	Device: cTBS Device: cathodal tDCS Device: sham **stimulation** 16 Years and older (Child, Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Outcomes Assessor)	Change in compound motor score slope at week 4 Change in alpha-band coherence between the affected motor cortex and the rest of the brain Change in Fugl Meyer Upper Extremity Motor Score at week 4
Robots Paired With tDCS in **Stroke** Recovery NCT01726673	Device: **Transcranial Direct** Current **Stimulation** (tDCS) Device: Placebo sham 18 Years and older (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Outcomes Assessor)	Fugl Meyer Assessment Score WOLF Motor Function Test (WMFT) Manual Muscle Test (MRC)
Transcranial Direct Current **Stimulation** and Robotic Therapy in Upper Limb Motor Recovery After **Stroke** NCT02496026	Device: tDCS plus wrist robot therapy Device: Sham tDCS plus wrist robot therapy 18 Years to 79 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)	Fugl-Meyer Motor Assessment Scale, Motricity Index; Modified Ashworth Scale Block and Box test
Dual Site-dual Channel Non-invasive Brain **Stimulation** for Motor Function in **Stroke** Patients NCT03486769	M1 **stimulation;** PMC **stimulation;** aIPS **stimulation** Behavioral: hand motor task 19 Years to 85 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Outcomes Assessor)	Changes in motor evoked potentia changes in nine hole peg test changes in grip and tip pinch strength test

Continuation of Table 2.

Study Title	Age/Interventions	Study Design	Outcome Measures
Association Between Brain **Stimulations** for the Rehabilitation of Chronic **Stroke** Patients NCT02817867	Device: tDCS Device: TMS Device: tDCS + TMS 18 Years to 85 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Investigator)	Wolf Motor Function Test Grip strength via hand dynamometer Manual Dexterity; Stroke Impact Scale
Effects of rTMS and tDCS on Motor Function in **Stroke** NCT01574989	Device: rTMS & tDCS 18 Years to 90 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Crossover Assignment Masking: Double (Participant, Outcomes Assessor)	Changes in cortical excitability measures Changes in motor function
Cortical Enhancement of Posture, Movement Planning, and Execution of Upright Reaching Following **Stroke** NCT04308629	Other: **Transcranial direct** current **stimulation** 40 Years and older (Adult, Older Adult)	Allocation: Randomized Intervention Model: Crossover Assignment Masking: Single (Participant)	Change in React response; Change in postural adjustments and reach onset Change in the reach onset (unit: seconds)
Effects of tDCS Combined With mCIMT or Mental Practice in Poststroke Patients NCT01879787	Other: tDCS 40 Years to 80 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Investigator)	Fugl-Meyer Assessment of Upper Extremity Motor Function; Motor Activity Log
Hybrid Approach to Mirror Therapy and **Transcranial Direct** Current **Stimulation** for **Stroke** Recovery NCT02254616	Behavioral: Mirror Therapy with real & tDCSsham-tDCS Behavioral: Mirror Therapy; Control Intervention 20 Years to 80 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Outcomes Assessor)	Change scores of Fugl-Meyer Assessment (FMA) Change scores of Wolf Motor Function Test (WMFT) Change scores of Motor Activity Log (MAL)
The Effect of The Five-Session Dual-tDCS On Lower-Limb Performance in Sub-Acute **Stroke** NCT04287231	Device: **Transcranial direct** current **stimulation** 18 Years to 75 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Factorial Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor)	Force distribution measurement (FDM; Timed-up and go test (TUG); Hand-held dynamometer (HHD)
Transcranial Galvanic **Stimulation** After **Stroke** NCT00407667	Device: **transcranial** galvanic **stimulation** 18 Years to 80 Years (Adult, Older Adults)	Allocation: Non-Randomized Intervention Model: Factorial Assignment Masking: Double (Participant, Investigator)	Fugl-Meyer Upper Limb Motor Score (0-66) Box&Block Test
Transcranial Direct Current **Stimulation** Combined Neuromuscular Electrical **Stimulation** on Motor Recovery in **Stroke** NCT04059848	Combination Product: tDCS & NMES 20 Years to 80 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Outcomes Assessor) Primary Purpose: Treatment	upper extremity subscale of Fugl-Meyer assessment Action Research Arm Test

doi: 10.7243/2055-2386-9-1

Continuation of Table 2.

Study Title	Age/Interventions	Study Design	Outcome Measures
tDCS and Physical Therapy in **Stroke** NCT00542256	Device: Active **tDCs** / CIMT Device: Sham **tDCs** / CIMT 18 Years to 80 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Outcomes Assessor)	Jebsen-Taylor Hand Function Test Motor Activity Log Rating Scale Beck Depression Inventory
Transcranial Stimulation in Motor **Stroke** Rehabilitation NCT02525393	Device: real &sham tDCS& rTMS 18 Years to 70 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Factorial Assignment Masking: Triple (Participant, Care Provider, Outcomes Assessor)	Change from the baseline ARAT; P300 (latency); standardized neuropsychological assessment)
tDCS on Motor Rehabiliation of Post **Stroke** Patients NCT03446378	Device: Anodal & cathodal tDCS Behavioral: Physical therapy 18 Years to 70 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Outcomes Assessor)	Fugl Meyer motor function Cortical excitability level ; Motor acitivy log - 30
Efficacy of a Combined **Transcranial Direct** Current **Stimulation** and Virtual Reality Intervention NCT03528018	Device: REACt system Other: Physical therapy 18 Years and older (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor)	Fugl-Meyer Assessment Scale Wolf Motor Function Test from baseline to the end of the intervention
Functional Interest of Non Invasive Brain **Stimulation** During Physiotherapy at a Subacute Phase Post **Stroke** (Anodal Protocol): ReSTIM NCT01500564	Device: anodal tDCS (device) Eldith DC-Stimulator Device: Sham tDCS 18 Years to 80 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Outcomes Assessor)	Fugl Meyer Assessment (Upper extremity) of motor recovery following stroke Functional independence scale (MIF) Motor Activity Log (MAL)
Enhancement of Motor Function With Reboxetine and **Transcranial Direct** Current **Stimulation** NCT00853866	Drug: reboxetine (palcebo& real) Device: tDCS Chronic; 18 Years to 86 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Crossover Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor)	Jebsen Taylor test maximum grip force nine hole peg test
Dextroamphetamine and tDCS to Improve the Fluency NCT02514044	Drug: Dexedrine Device: Active tDCS Behavioral: Speech Therapy 18 Years and older (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Outcomes Assessor)	Percent Change in Language Quotient as Assessed by the Western Aphasia Battery Percent Change in Aphasia Quotient as Assessed by the Western Aphasia Battery
Transcranial Direct Current **Stimulation** Associate to Constraint Induced Movement Therapy Over Premotor Cortex in Severe **Stroke** NCT02628561	Device: **Transcranial direct** current **stimulation** Behavioral: Constraint-Induced Movement Therapy 18 Years to 65 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	FIM, Barthel Index Modified Ashworth Scale Muscle strength (Medical Research Council Scale)

Continuation of Table 2.

Study Title	Age/Interventions	Study Design	Outcome Measures
Impact of Non-invasive Brain **Stimulation**, Associated With Upper Limb Robot-assisted Therapy, on Motor Recuperation NCT02512289	Device: tDCS (ELDITH) and RAT (REAplan) 18 Years to 90 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Crossover Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	Upper Limb Kinematics Box and Block test Purdue Pegboard Test
Late LTP-like Plasticity Effects of tDCS in Chronic **Stroke** Patients NCT02399540	Device: Sham Device: Conventional Paired tDCS Device: Conventional Unpaired tDCS Device: Late LTP-like Plasticity tDCS 18 Years to 79 Years (Adult, Older Adult)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	Motor Skill Retention Maximum Grip Force Purdue Pegboard Test

promote adaptive plasticity in the stroke population with significant enhancement of premotor, somatosensory and motor execution areas. In a review by Bornheim et al 2020 two databases (Medline & Scopus) were searched for randomized, double-blinded, sham-controlled trials pertaining to the use of M1 tDCS (20 min of stimulation, at 2 mA with 25 or 35cm^2 electrodes) on stroke patients, and its effects were validated on functional motor outcomes. 46 studies with (n=1291 patients) met inclusion criteria. 71.7% of studies found that tDCS has positive results on functional motor outcomes with an ES between 0-1.33 [34]. A randomized controlled trial with combination of tDCS and CIMT led to improvement in FMA, MAL and hand grip scores; the anodal tDCS seems to have greater impact than the cathodal tDCS in increasing the mCIMT effects on motor function of chronic stroke patients. We share our experience with the University of Buffalow (USA) and studied the efficacy of cerebellar transcranial direct current stimulation (ctDCS) of the dentate nuclei to observe standing balance in chronic (>6 months post-stroke) stroke survivors. This pilot study presented promising results on the beneficial effects of deep ctDCS on functional reach during a standing balance task in chronic stroke survivors [35].

A multicentric trial is underway from our institute to study the role of Fluoxetine or tDCS and /or combination therapy with drug & device (Fluoxetine & tDCS) on postural Stability and gait in stroke patients between 1 -6 months of index event. All subjects had undergone 12 sessions of tDCs with each session lasting 20 minutes. This was followed by 2 extra sessions every other week of active tDCS with session lasting 20 minutes. Additionally, subjects also took placebo or active fluoxetine by mouth two hours before the tDCS and exercise regime. Placebo fluoxetine tablet was identical in form, colour, and odor and packaging. Exercise regime began within 1 hour after each bihemispheric sham tDCS session and lasted for 45 minutes. As it is RCT (CTRI/2017/05/008668) the results of the study are awaited and one of the abstract got published in World Congress of neurorehabilitation congress 2018 [36].

NIBS and newer imaging technologies

Merging NIBS with other brain-imaging techniques provides particularly powerful means to explore brain function in the living human brain, understand brain-behavior relations and optimize the impact of brain stimulation techniques. A non invasive, method to measure the neuroenergetic status of the cortex is assessed through near infrared spectroscopy (NIRS-EEG joint-imaging sensor montages. These are capable of measuring optical changes in tissue brought about by hemoglobin concentration changes. (NIRS) is one technique that studies brain hemoglobin levels in the coil region pre and post NIBS stimulation. A few authors extended the conventional NIRS technique by increasing the number of light emitter and detector pairs (a single pair is normally used in NIRS) [37].

This review focuses on NIBS and stroke with special mention to upper limb function vis a vis other deficits like pain, aphasia, lower limb dysfunction and sensory syndromes. It is apparent that the best intervention for stroke recovery will incorporate a combination of techniques to maximize neuronal plasticity. The usage and efficacy of these modalities is barred by several factors which stroke is associated with like topography, lesion location and pattern, time course post stroke, the type of adjuvant therapy administered and the most of all the stimulation characteristics. A recent Cochrane review suggests that there is very little enhancement of motor activity when NIBS is used alone [37]. Most of our trials were combination therapy with tDCS & TMS with physical or occupational therapy. Our experience elegantly state that TMS is effective in acute and subacute stages of ischemia whereas TDS is relatively a good option for chronic stroke.

Competing interests

The authors declare that they have no competing interests.

Acknowledgement

AB designed the manuscript, NK helped in edits and formatting, SSK and MVP reviewed the line up of manuscript.

Authors' contributions

Authors' contributions	AB	NK	MVP	SSK
Research concept and design	√	--	--	--
Collection and/or assembly of data	--	√	--	--
Data analysis and interpretation	√	--	--	--
Writing the article	√	√	--	--
Critical revision of the article	--	--	√	√
Final approval of article	--	--	√	√
Statistical analysis	√	--	--	--

Publication history
Editor: Catherine Ortega, University of Texas Health Science Center, USA.
Received: 05-April-2022 Final Revised: 30-June-2022
Accepted: 04-July-2022 Published: 09-July-2022

References

1. Williams JA, Imamura M, Fregni F. Updates on the use of non-invasive brain stimulation in physical and rehabilitation medicine. J Rehabil Med 2009; 41:305–311.
2. Fregni F, Pascual-Leone A. Technology Insight: noninvasive brain stimulation in neurology—perspectives on the therapeutic potential of rTMS and tDCS. Nature. Clin Pract Neurol 2007 Jul;3(7):383-93
3. Najib U, Shahid Bashir S, Dylan Edwards D, Rotenberg A, Pascual-Leone A. Transcranial Brain Stimulation: Clinical Applications and Future Directions. Neurosurg Clin N Am. 2011;22(2):233–239.
4. Ruiz ML, Sarasa ML, Rodriguez SL, Leon JB, Ristol GA, Arce SA. Current evidence on transcranial magnetic stimulation and its potential usefulness in post-stroke neurorehabilitation: Opening new doors to the treatment of cerebrovascular disease. Neurología. 2017;33(7):459-472.
5. Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. Lancet Neurol. 2003;2:145-156.
6. Kang N, Summers J, Cauraugh JH. Review: Transcranial direct current stimulation facilitates motor learning post-stroke: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2016;87:345–355.
7. Demirtas-tatlidede A, Alonso-alonso M, Shetty RP, Ronen I, Alvaro P-L, Fregni F. Long-term effects of contralesional {rTMS} in severe stroke: safety, cortical excitability, and relationship with transcallosal motor fibers. NeuroRehabilitation 2014;36:51–9.
8. Caro SO, Khalil AA, Sehm B, Villringer A, Nikulin VV, Nazarova M. Predicting the response of non invasive brain stimulation in stroke. Frontiers in Neurol 2019; 10:article 302.
9. Di Pino G, Pellegrino G, Assenza G, Capone F, Ferreri F, Formica D, et al. Modulation of brain plasticity in stroke: a novel model for neurorehabilitation. Nat Rev Neurol. (2014) 10:597–608. doi: 10.1038/nrneurol.2014.162
10. Grefkes C, Ward NS. Cortical reorganization after stroke: how much and how functional? Neuroscientist. 2014;20:56–70.
11. Morishita T, Hummel FC. Non-invasive brain stimulation (NIBS) in motor recovery after stroke: concepts to increase efficacy. Curr Behav Neurosci Rep. 2017;4:280–9
12. Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD. Interhemispheric inhibition of the human motor cortex. J Physiol 1992;453:525.
13. Li LM, Violante IR, Leech R, Ross E, Hampshire A, Opitz A, et al. Brain state and polarity dependent modulation of brain networks by transcranial direct current stimulation. Hum Brain Mapp. 2019;40:904–15.
14. Pratik Y. Chhatbara, Viswanathan Ramakrishnanb, Steven Kautzc,d, Mark S. Georged,e, Robert J. Adamsa, and Wuwei Feng. Transcranial Direct Current Stimulation Post-Stroke Upper Extremity Motor Recovery Studies Exhibit a Dose–Response Relationship. Brain Stimul. 2016;9(1):16–26.
15. Lazzaro V, Oliviero A, Profice P, Insola A, Mazzone P, Tonali P, et al. Direct demonstration of interhemispheric inhibition of the human motor cortex produced by transcranial magnetic stimulation. Experimental brain research. 1999;124:520–524
16. Deng Z, Lisanby SH, Peterchev AV. Coil Design Considerations for Deep Transcranial Magnetic Stimulation.Clinical Neurophysiol 2014; 125(6):1202-1212.
17. Ackerley SJ, Stinear CM, Barber PA, Byblow WD. Combining theta burst stimulation with training after subcortical stroke. Stroke 2010;41:1568–72
18. Chung SW, Hill AT, Rogasch NC, Hoy KE, Fitzgerald, PB. Use of theta-burst stimulation in changing excitability of motor cortex: a systematic review and meta-analysis. Neurosci. Biobehav. Rev. 2016;63: 43–64.
19. Zhang L, Zing G, Fan Y, Guo Z, Chen H, Mu Q. Short- and Long-term Effects of Repetitive Transcranial Magnetic Stimulation on Upper Limb Motor Function after Stroke: a Systematic Review and Meta-Analysis. Clinical Rehabil 2017;31(9):1137-1153.
20. Dionisio A, Duarte CI, Patricio M, Branco MC. The Use of Repetitive Transcranial Magnetic Stimulation for Stroke Rehabilitation: A Systematic Review. J of Stroke & Cerebrovascular Dis 2018;27(1):1-31
21. Nitsche MA, Liebetanz D, Schlitterlau A, Henschke U, Fricke, K, Frommann K, et al . GABAergic modulation of DC stimulation-induced motor cortex excitability shifts in humans. The European journal of neuroscience. 2004;19(10):2720–2726.
22. Xiang H, Sun J, Tang X, Zeng K, Wu X. The effect and optimal parameters of repetitive transcranial magnetic stimulation on motor recovery in stroke patients: a systematic review and meta-analysis of randomized controlled trials. Clinical Rehabil 2019;33(5):847-864.
23. Lefaucheur, J. P., André-Obadia, N., Antal, A., Ayache, S. S., Baeken, C., Benninger, D. H., et al. (2014). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin. Neurophysiol. 2014;125:2150–2206.
24. Auriat AM, Neva JL, Peters S, Ferris JK, Boyd LA. A review of transcranial magnetic stimulation and multimodal neuroimaging to characterize post stroke neuroplasticity. Frontiers in Neurology 2015; 6:226-232.
25. Neha Kuthiala, Ashu Bhasin, Rahul Sharma, M V Padma Srivastava S Senthil Kumran, Sakshi Sharma and Nand Kumar. rTMS and CIMT for Neurofunctional Recovery in Chronic Stroke. Int J Neurorehabilitation Eng 2020;7:6-13.
26. Sharma H, VY V, Kumar N, Sreenivas V, Rajeshwari MR, Bhatia R, Sharma R, Srivastava MVP. Efficacy of Low-Frequency Repetitive Transcranial Magnetic Stimulation in Ischemic Stroke: A Double-Blind Randomized Controlled Trial. Archives of Rehabilitation Research and Clinical Translation 2020; 2(1);1-10.
27. Srivastava MP, Kuthiala N. Restorative Therapies after stroke: Drugs, Devices and Robotics. Annals Natl Acad Med Sci 2019;55:124–13.
28. Schlaug G, Renga V, Transcranial Direct Current Stimulation in Stroke Recovery. Arch Neurol 2008;65(12):1571-1576.
29. Wagner T, Fregni F, Fecteau S, Grodzinsky A, et al. Transcranial direct current stimulation: a computer-based human model study. Neuroimage. 2007;35(3):1113–24
30. Marquez J, van Vliet P, McElduff P, Lagopoulos J, Parsons, M. Transcranial direct current stimulation (tDCS): does it have merit in stroke rehabilitation? A systematic review. Int. J. Stroke 2015;10:306–316.
31. Elsner B, Kugler J, Pohl M, Mehrholz J. Transcranial direct current stimulation (tDCS) for improving activities of daily living, and physical and cognitive functioning, in people after stroke. Cochrane Database Syst Rev 2016;3:CD009645.

32. Orru G, Coversano C, Hitchkott PK, Gemignani A. Motor stroke recovery after tDCS: a systematic review. Reviews in the Neurosciences 2020;31;2:201–218.

33. Bornheim S, Thiabuat A, Beaudart C, Macquet P, Croisier JL, Kuax JF. Evaluating the effects of tDCS in stroke patients using functional outcomes: a systematic review. Disabil Rehabil 2020 May 12;1-11.

34. Rocha S, Silva A, Foerster A, Wiesiolek C, Chagas AP, Machado G, Baltar A. The impact of transcranial direct current stimulation (tDCS) combined with modified constraint-induced movement therapy (mCIMT) on upper limb function in chronic stroke: a double-blind randomized controlled trial. Disabil Reahbil 2016;38(7):653-60.

35. Razayee Z, Kaura S, Solanki D, Dash A, Srivastava MVP, Lahiri U, Dutta A. Deep Cerebellar Transcranial Direct Current Stimulation of the Dentate Nucleus to Facilitate Standing Balance in Chronic Stroke Survivors-A Pilot Study. Brain Sci 2020;10(2):94-101.

36. Roy B, Srivastava MVP, Bhatia R, Kumar N, Wadhwa S. Effect of Dual-Task Exercise in Conjunction with Fluoxetine & Transcranial Direct Current Stimulation on Postural Stability and Gait in Stroke Patients. Neurorehabilitation and Neural Repair 2018;32(4-5):317–323. (WCNR 2018 Oral abstracts).

37. Elsner B, Kugler J, Pohl M, Mehrholz J. Transcranial direct current stimulation (tDCS) for improving activities of daily living, and physical and cognitive functioning, in people after stroke (Review). Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd. . Cochrane Database of Systematic Reviews 2016, Issue 3. Art. No.: CD009645.

Citation:
Bhasin A, Kuthiala N, Srivastava MVP and Kumaran SS. **Non-Invasive Brain Stimulation in Stroke- Our Experience and an Overview**. *Phys Ther Rehabil*. 2022; **9**:1.
http://dx.doi.org/10.7243/2055-2386-9-1