Summary of Findings

Research question: Under what medical therapies following a stroke do we see increased plasticity in the human brain?

**Introduction**

Neuronal plasticity often plays a major role in medical interventions directed towards recovery of motor function in stroke victims. This systematic review will assess the validity and significance of several medical interventions conducted on stroke patients within randomized controlled trial (RCT) studies and their ability to promote neuronal plasticity. Assessment of these studies should provide valuable insight into the most effective procedures towards recovery of motor function through Neuronal plasticity, as well as clarifying the best conditions in which plasticity may be promoted in the brains of individuals who have suffered from strokes.

An initial review protocol was created to determine the fundamentals and scope for the review, which was followed by a Searching and Screening Protocol to find and narrow down the number of studies to a reasonable amount to be assessed by the team. The remaining 16 papers were divided between the team and critical information was extracted and organized into a table. Data was extracted and synthesized, identifying important trends and themes across the studies.

**Summary of search and screening results**

We utilized an iterative search process to find results, increasing search specificity until we had 79 results (Appendix A). We took the 54 top results from the search and did an initial screening of titles and abstracts. Many studies were excluded for having sample sizes under our minimum of 20 participants or having an observation period of less than one month. Afterwards, we performed full-text analyses on the remaining documents, removing those which did not meet our criteria, to a final total of 16 results (Appendix B). These studies mainly used 2 types of intervention, electrical brain stimulation and physiotherapy/robotics. Most of these focused on promoting neural plasticity to assist in regaining physical function. They were all randomized controlled trials typically with more elderly populations published within the past 20 years and could be accessed through PubMed.

**Data extraction table and study characteristics**

Table – Appendix C, Appendix D

The studies we pursued were all randomized controlled trials, with a mix of double and single blinded experiments. They were published across a variety of countries, typically within the last five years. They typically had 20-50 subjects with a variety between ischemic and hemorrhagic strokes. Exclusion criteria for the studies included other severe cardiac, cognitive, or respiratory disorders which would influence the results. In some cases, additional factors such as smoking or certain medications were also grounds for exclusion. Most studies had even ratios between men and woman, with populations typically in the age range of 40-80, with some exceptions. There were some commonalities in the methods of assessment of therapeutic effectiveness, with some tests such as the Fugl-Meyer Assessment being common across many studies, though each typically included unique methods as well. Observation and treatment periods varied between a few days to several months of treatment with at least a month of observation. The means of treatment had some commonality, with transcranial direct current stimulation and robot-assisted physical therapy being the most common interventions, with a few additional methods. Within these therapies, some variation existed between factors such as scheduling, testing and means of applying techniques.

**Synthesis of the findings**

The most common treatment to improve neural plasticity following a stroke within our review was Transcranial Direct Current Stimulation (TDCS), or occasionally Transcranial Magnetic Stimulation (TMS). This method hoped to increase activation of neurons which may have been damaged by the stroke by electric stimulation. One difficulty in many of these therapies was creating a sham trial, as subjects could determine the presence or lack of the therapy [6]. Exclusion criteria also varied from tight age ranges to medical conditions. Such method prompts improvements in recovery rates after strokes, seen in increased motor skill learning. For example, one study [16] testing a control group and a TDCS group found that TDCS catalyzed the improvement of motor skills. This was proven true by many other studies, as well as through tests including the JTT [9], FNT [15], BBT [10], though not all studies due to causes such as minimal measurement rigor [14]. With this type of intervention specific methods vary. As the therapy is electrically based, frequency and intensity are subject to change. Frequency of pulses can vary from 1 Hz [14] to 50 Hz [12] in the typical intensities of microvolts [10] (though such processes were tailored to subject comfort [6]. In general, TDCS proved an effective means by which to promote neural plasticity.

Regarding training involving robotics, a common trend was proprioception, which is one’s ability to sense the movement of one’s own body or appendages. Several studies [5,10] attempted to determine the importance of proprioceptive exercises, which encouraged willful intent from participants in the training of appendages affected by the stroke, in evoking neuroplasticity. A study [10], used a novel testing procedure to gauge a participant’s proprioceptive ability by having the robotic device move their middle and index fingers 12 times at different trajectories, while the participant’s vision was impaired, and they were required to hit a button when they felt their fingers overlap. The results of the study showed that a participant’s baseline proprioceptive ability acted as a predictor for improvement in the motor function tests such as the Box and Blocks Test (i.e. better proprioceptive ability leads to larger improvements in motor function). Other studies [3, 5, 11] discuss the importance of proprioceptive feedback for sensorimotor integration and cortical motor learning. Robotic assistance has great potential benefits for detecting and training proprioception, which could lead to a more effective promotion of neural plasticity and regained motor function.

Though most of the studies related to improvement in physical performance to upper limb function using a combination of physiotherapy and additional treatments, some took a different approach. One study [8] utilized hyperbaric oxygen chambers to increase oxygen flow to the brain and promote neural plasticity. One limitation of that method was its inability to properly create a sham trial, as hyperbaric conditions without an increase in oxygen are considered unethical. As such, that study utilized a cross trial instead. However, it still found improvements in both groups after the trial, with scans showing lesions visually disappearing as brain activity increased in those areas and questionnaire scores increasing [9]. Another study [7] used similar nervous stimulation methods to TDCS but focused on the throat and mouth as a means of ameliorating dysphagia conditions. That study found small differences in recovery rates between its sham and treated group. This was also due to insufficient treatment time, with only 3 sessions over 3 days. As such, strategies like this one would result in greater advancement in stroke recovery if tested over a longer period like those previously discussed. Thus, while other methods are yet unproven, new avenues are open for further innovation.

**Discussion/conclusion**

From a survey of the research, electrical stimulation seems to prompt improvement in limb function, particularly when paired with additional physical training. Robotic assistance training also proved effective, providing avenues to improve areas where conventional training is insufficient. Other therapies had mixed results, with hyperbaric oxygen giving promising results but direct stimulation of Pharyngeal glands being inconclusive. Such instances demonstrate the importance of treatment periods, with the most effective treatments taking place over longer durations. Most studies had small sample sizes and observation times but were accepted to avoid excluding too many potential studies from the review.

There are several tangentially related topics found during the review, which could act as valuable sources of inquiry for future investigation like hyperbaric oxygen or proprioception. Since the initial research question was narrowed down, other branches in the field of neuroplasticity could also be examined in the future, like music or neuromodulation. Periodic assessments of new, larger studies would be useful in remaining consistent with academic consensus.

An ideal new research trial could be conducted within a hospital, where it is easier to monitor participants’ movements and usage of appendages affected by the stroke. The population could be limited, specifically to patients suffering from ischemic strokes, and the age range could be kept to participants ages 50-60 to reduce the risk of degradation of neuroplasticity over time. We propose a trial involving 2 groups (with a control group), with one receiving TDCS while the other receiving physiotherapy with robotic aid to measure exactly which medical intervention would best promote neuroplasticity.

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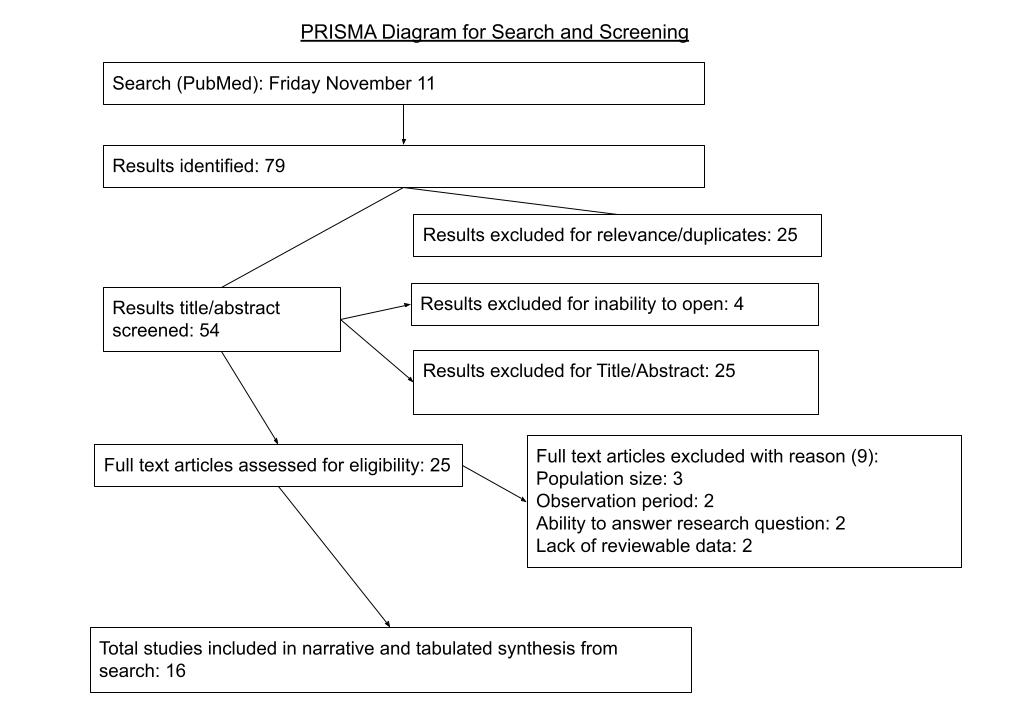
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**Appendix**

Appendix A. Prisma Flow Diagram



Appendix B. Sources from diagram

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Source** | **Title** | **Author** | **Year** | **Link** |
| **1** | **Constraint Induced Movement Therapy Increases Functionality and Quality of Life after Stroke** | **Larissa Salgado Oliveira Rocha et al** | **2021** | [**https://www.sciencedirect.com/science/article/pii/S1052305721001774**](https://www.sciencedirect.com/science/article/pii/S1052305721001774) |
| **2** | **Effect of Cerebellar Stimulation on Gait and Balance Recovery in Patients With Hemiparetic Stroke: A Randomized Clinical Trial** | **Giacomo Koch et al** | **2018** | [**https://pubmed.ncbi.nlm.nih.gov/30476999/**](https://pubmed.ncbi.nlm.nih.gov/30476999/) |
| **3** | **Evidence of neuroplasticity with robotic hand exoskeleton for post-stroke rehabilitation: a randomized controlled trial** | **Neha Singh et al** | **2021** | [**https://pubmed.ncbi.nlm.nih.gov/33957937/**](https://pubmed.ncbi.nlm.nih.gov/33957937/) |
| **4** | **Brain-actuated functional electrical stimulation elicits lasting arm motor recovery after stroke** | **A Biasiucci et al** | **2018** | [**https://pubmed.ncbi.nlm.nih.gov/29925890/**](https://pubmed.ncbi.nlm.nih.gov/29925890/) |
| **5** | **Shaping neuroplasticity by using powered exoskeletons in patients with stroke: a randomized clinical trial** | **Rocco Salvatore Calabro et al** | **2018** | [**https://pubmed.ncbi.nlm.nih.gov/29695280/**](https://pubmed.ncbi.nlm.nih.gov/29695280/) |
| **6** | **Effect and Safety of Transcutaneous Auricular Vagus Nerve Stimulation on Recovery of Upper Limb Motor Function in Subacute Ischemic Stroke Patients: A Randomized Pilot Study** | **Dandong Wu et al** | **2020** | [**https://pubmed.ncbi.nlm.nih.gov/32802039/**](https://pubmed.ncbi.nlm.nih.gov/32802039/) |
| **7** | **Pharyngeal Electrical Stimulation in Dysphagia Poststroke: A Prospective, Randomized Single-Blinded Interventional Study** | **Dipesh H Vasant et al** | **2016** | [**https://pubmed.ncbi.nlm.nih.gov/27053641/**](https://pubmed.ncbi.nlm.nih.gov/27053641/) |
| **8** | **Hyperbaric oxygen induces late neuroplasticity in post stroke patients--randomized, prospective trial** | **Shai Efrati et al** | **2013** | [**https://pubmed.ncbi.nlm.nih.gov/23335971/**](https://pubmed.ncbi.nlm.nih.gov/23335971/) |
| **9** | **Hebbian-Type Primary Motor Cortex Stimulation: A Potential Treatment of Impaired Hand Function in Chronic Stroke Patients** | **Kate Pirog Revill et al** | **2020** | [**https://pubmed.ncbi.nlm.nih.gov/31976804/**](https://pubmed.ncbi.nlm.nih.gov/31976804/) |
| **10** | **Robotic Assistance for Training Finger Movement Using a Hebbian Model: A Randomized Controlled Trial** | **Justin B Rowe et al** | **2017** | [**https://pubmed.ncbi.nlm.nih.gov/28803535/**](https://pubmed.ncbi.nlm.nih.gov/28803535/) |
| **11** | **Neuroplastic effects of end-effector robotic gait training for hemiparetic stroke: a randomised controlled trial**  **Neuroplastic effects of end-effects** | **Hayeon Kim et al** | **2020** | [**https://pubmed.ncbi.nlm.nih.gov/32719420/**](https://pubmed.ncbi.nlm.nih.gov/32719420/) |
| **12** | **High-frequency versus theta burst transcranial magnetic stimulation for the treatment of poststroke cognitive impairment in humans** | **Tsai PY et al** | **2020** | [**https://pubmed.ncbi.nlm.nih.gov/32159313/**](https://pubmed.ncbi.nlm.nih.gov/32159313/) |
| **13** | **Comparison of Neuroplastic Responses to Cathodal Transcranial Direct Current Stimulation and Continuous Theta Burst Stimulation in Subacute Stroke** | **Nicolo P et al** | **2018** | [**https://pubmed.ncbi.nlm.nih.gov/29223708/**](https://pubmed.ncbi.nlm.nih.gov/29223708/) |
| **14** | **Low-Frequency Repetitive Transcranial Magnetic Stimulation Over Contralesional Motor Cortex for Motor Recovery in Subacute Ischemic Stroke: A Randomized Sham-Controlled Trial** | **Won-Seok Kim et al** | **2020** | [**https://pubmed.ncbi.nlm.nih.gov/32807013/**](https://pubmed.ncbi.nlm.nih.gov/32807013/) |
| **15** | **Transcranial electrostimulation with special waveforms enhances upper-limb motor function in patients with chronic stroke: a pilot randomized controlled trial** | **Shih-Ching Chen et al** | **2021** | [**https://pubmed.ncbi.nlm.nih.gov/34193179/**](https://pubmed.ncbi.nlm.nih.gov/34193179/) |
| **16** | **Transcranial Direct Current Stimulation Enhances Motor Skill Learning but Not Generalization in Chronic Stroke** | **Manuela Hamoundi et al** | **2018** | [**https://pubmed.ncbi.nlm.nih.gov/29683030/**](https://pubmed.ncbi.nlm.nih.gov/29683030/) |

Appendix C. Link to data extraction table

<https://utoronto-my.sharepoint.com/:x:/r/personal/janoshan_satsoruban_mail_utoronto_ca/_layouts/15/Doc.aspx?sourcedoc=%7B396354be-a01b-4ca5-ac16-25c5734ec51f%7D&action=editnew>

Appendix D. Data extraction table (ordered the same as reference list)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No. | Study Name | Year | Country | Study type | Sample size with control/sham | Population age ranges | Gender distribution | Inclusion criteria (stroke type, area, time since stroke) | Exclusion Criteria (previous conditions, baseline assessment, anything else listed) | Type of intervention with details (tcds, brain area, hyperbaric, frequency, area targeted, etc) | Intervention length and schedule | Observation times | Measurement method | Results for tests baseline and studied | Additional notes |
| 1 | Constraint Induced Movement Therapy Increases Functionality and Quality of Life after Stroke | 2021 | Brazil | Double blind | n=70 tested for eligibility  n=30 included in study  n=15 in control group  n=15 in constraint induced movement therapy group | 45-80 | N/A | Age group 45 to 80 years old  Both sexes  Clinical diagnosis of stroke  Time of injury above six months | Score above 24 points in the Mini State Exam Mental | Therapy was constraint induced physiotherapy, with the healthy portion of the limb secured to force the use of the damaged portion over a series of household tasks, 5 minutes each for 60 minutes | 24 sessions over 8 weeks, thrice a week | After the 12th and 24th session (1 month and 2 months) | FMA  SSQOL  FRT (functional reach test)  Modified Ashworth | Reduction in muscle tone (resistance) in muscles relative to baseline  FMA scores increased, indicating its effects on cortical reorganization | Suggest a combination of more functional activities in future research  Also warns of risks of greater injury if treatments are too intense |
| 2 | Effect of Cerebellar Stimulation on Gait and Balance Recovery in Patients With Hemiparetic Stroke: A Randomized Clinical Trial | 2018 | Italy | Double blind | n=52 tested for eligibilty  n=36 included in study  n=18 allocated to iTBS  n=18 allocated to sham  n=2 lost to follow-up | 60- 70 | Male:Female=21:13 | First ever chronic ischemic stroke  Hemiparesis due to left or right subcortical or cortical lesion in the territory of the middle cerebral artery  Residual gait and balance impairment | History of seizures  Severe general impairment or concomitant diseases  Patients older than 80 years  Treatment with benzodiazepines, baclofen, and antidepressants | Patients were randomly assigned to treatment with CRB-iTBS or sham iTBS applied over the cerebellar hemisphere ipsilateral to the affected body side immediately before physiotherapy | Daily during 3 weeks | March 2013- June 2017 | BBS  FMA  BI  Gait Analysis | Patients treated with CRB-iTBS but not with sham iTBS showed an improvement of gait and balance functions | Treatment of tendency to fall considered highly valuable, as it typically declines into a long term disability in stroke patients  No neurological changes noticed in areas in unaffected hemispheres, allowing the treatment to specifically target areas  Small sample size |
| 3 | Evidence of neuroplasticity with robotic hand exoskeleton for post-stroke rehabilitation: a randomized controlled trial | 2021 | India | Double blind | n > 300 tested for eligibility  n = 27 clinical assessment  n = 13 in Robotic-therapy Group  (n = 3 dropouts)  n = 14 in in Control-Group  (n = 1 dropout)  n = 12 in Robotic-therapy Group  n = 13 in in Control-Group | 30.8-53.0 | Male:Female = 19:4 | Ischemic / Hemorrhagic stroke  Single lesioned  Cortical / Subcortical Stroke  Stroke onset = 3-24 months  Age = 18-70  MMSE Score = 24-30 | Incompatible with TMS  Physical, social and economic constraints  Having Craniotomy, Aphasia or cognitive issue  Age > 70  No spasticity at 3 months | Evaluate the effects of a novel exoskeleton based therapy on the functional rehabilitation  outcomes of upper-limb and cortical-excitability in patients with stroke as compared to  the conventional-rehabilitation | 20 sessions of 45 min each  5 days a week | 4 weeks | MRI  MAS  FMA  BI  BS  Range of motion | Robotic-exoskeleton training showed improvement  in motor outcomes and cortical-excitability in  patients with stroke. Neurophysiological changes  in RG could most likely be a consequence of  plastic reorganization and use-dependent plasticity. | Limitations:  -Small sample size  -Lack of an activity level measurement like Wolf Motor Function test and Action Research Arm Test  -No midterm clinical assessment  -No long term follow-up of patients |
| 4 | Brain-actuated functional electrical stimulation elicits lasting arm motor recovery after stroke | 2018 | Switzerland | Double blind | n = 27 | 36-76 | Male: 16  Female: 11 | Age > 18  Minimum 10 months from stroke  Moderate-to-severe disability  Severe hand paralysis with a FMA-UE score ≤ 40 points  Good or corrected eyesight | Factors hindering EEG acquisition (e.g., skin infection)  Heavy medication affecting the central nervous system  Concomitant serious illness (e.g., fever)  Unilateral spatial neglect  Neurological disorders (e.g., Parkinson’s disease)  Severe or recent heart disease | Motor areas in the affected hemisphere | Clinical evaluations were performed immediately before  and after the intervention, as well as 6–12 months  after the end of the intervention (average 36 weeks) | Groups received therapy two times per week for a  period of 5 weeks each session lasting 60 min | MRI  Mixed-design ANOVA statistical tests  MRS  MRC  Electroencephalography analysis | Results illustrate how a BCI–FES  therapy can drive significant functional recovery and purposeful plasticity thanks to contingent activation of body natural efferent and afferent pathways. | Limitations:  - Did not check for any placebo effect that could have influenced patients  - The limited accuracy and repeatability of hand movements generated by FES |
| 5 | Shaping neuroplasticity by using powered exoskeletons in patients with stroke: a randomized clinical trial | 2018 | Italy | Double blind | n = 58 Assessed for eligibility  n = 18 Excluded  n = 40 Were analysed | 57-76 | M: 23  F: 17 | Age >= 55  Suffering from a first, single ischemic supra-tentorial stroke  Muscle Research Council score of ≤3  Mini-Mental State Examination of > 24  Functional Ambulatory Categories of ≤ 4  MAS of ≤2 | Had to meet the inclusion/exclusion criteria of  the manufacturer’s recommendations | Forty patients in a prospective, pre-post, randomized clinical study were tested.  Twenty patients underwent Ekso™ gait training (EGT) (45-min/session, five times/week), in addition to overground gait therapy, whilst 20 patients practiced an OGT of the same duration. All individuals were evaluated about gait performance (10 m walking test), gait cycle, muscle activation pattern (by recording surface electromyography from lower limb muscles), frontoparietal effective connectivity (FPEC) by using EEG, cortico-spinal excitability (CSE), and sensory-motor integration (SMI) from both primary motor areas by using Transcranial Magnetic Stimulation paradigm before and after the gait training. | Conventional physiotherapy training: Five sessions per week for eight consecutive weeks, 60 min for each session.  In addition to conventional physiotherapy training, EGT patients practiced 45-min session of Ekso training,  while OGT patients underwent 45-min of conventional gait training, for all 8 weeks. | 8 Weeks | MCID  TMS  SMI  CSE | Ekso™ could be useful to promote mobility in persons  with stroke owing to mechanisms of brain plasticity  and connectivity re-modulation that are specifically  entrained by the robotic device, as compared to conventional OGT. | Limitations:  -Lack of long-term follow-up evaluation |
| 6 | Effect and Safety of Transcutaneous Auricular Vagus Nerve Stimulation on Recovery of Upper Limb Motor Function in Subacute Ischemic Stroke Patients: A Randomized Pilot Study | 2020 | China | Single blind | n=23 tested for eligibility n=2 declined to participate n=10 in taVNS group n=11 in sham taVNS group | 51-75 | Male:Female = 13:8 | First time ischemia stroke  Between 0.5 and 3 months post onset  Single upper limb motor function impairment  No obvious cognitive impairment | Hemorragic stroke, leading to lesion etiology heterogeneity  Advanced cardiac, pulmonary, liver, or blood disease  Malignant tumors  Infectious disease  Unrelated neurological or musculoskeletal disease  Heart rate under 60bpm  Previous surgery on the vagus nerve  Botox injections on upper extremeties | taVNS  Left auricular branch vagus nerve stimulated by the modified dot-like electrodes that were fitted to the cymba conchae  600 pulses at 20Hz every 5 minutes  Intensity subject to tolerance  Performed 30 minutes a day for 15 consecutive days  Also performed physical rehabilitation for 30 mins after each taVNS session | Daily taVNS and physical training sessions for 15 days  Physical training included postural control, proprioception exercises, neuromuscular facilitation, and gait training | 15 days, 4 weeks and 12 weeks | FMA-U  WMFT  FIM  Brunnstrom | All measures increased after the 15 days, typically with twice as great an increase as in the sham group  Brunnstrom test was similar between the two groups after 15 days  FMA-U increase remained about double versus sham group at 4 weeks and 12 weeks, though did decrease slightly at 12 weeeks. | Limitations  Lack off measuremennt of other scores at later observation periods  Study believes the effect of taVNS may decrease over time, with FMA scoures at 12 weeks slightly lower than those at 8 weeks  Sham group did not receive electric stimulation, meaning participants were not blinded |
| 7 | Pharyngeal Electrical Stimulation in Dysphagia Poststroke: A Prospective, Randomized Single-Blinded Interventional Study | 2016 | UK | Single blind | n=516 assessed  n = 38 baseline evaluated  n = 36 randomised  n = 36 assessed at 2 weeks  n = 35 assessed at 3 months | 56-79 | Male:female=22:14 | Newly onset Dysphagia(swallowing difficulties)  Within 6 months of hemorragic or ischemic stroke  Failed VFS or FEES | Advanced dementia  Other neurological conditions which could influence dysphagia  Previous history of dysphagia  Patients had been intubated/trachiotomized  Pacemaker or internal defribulator  Tumors  Severe cardiac or respiratory conditions  Structural anomalies in mouth or throat  Required continuous oxygen supply | Pharyngeal electrical stimulation  Intraluminnal pharyngeal stimulation catheter  Inserted orally or nasally  0.2ms pulses at 280V, 5Hz frequency with patient determined intensity thresholds  Standard swallowing treatments as determined by patient hospitals  10 minutes a day for 3 days | Pharyngeal electrical stimulation 10 minutes a day for 3 days | Baseline swallowing test  2 week DSR/VFS/FEES test  3 month DSR/VFS/FEES test | Toronto bedside Swallowing Screening Test (TOR-BSST)  Dysphagia Severity rating (DSR)  Fiberoptic endoscopic examination (FEES) of swallowing)  Video fluroscopic swallowing test (VFS) | 11% more patients had no/mild dysphagia after 2 weeks (61% to 50%)  1 patient in sham had worse dysphagia, none in treated  78% had no/mild in treated at 3 months, 76% in control  39 to 52 days in hospital discharge times for treated and control | Limitations/notes  Low time spent on treatment makes its effectiveness inconclusive  Authors do suggest data suggests an effect, but does not prove one  Suggests that treatment is most effective early on, as swallowing seems to be regained eventually naturally |
| 8 | Hyperbaric oxygen induces late neuroplasticity in post stroke patients--randomized, prospective trial | 2013 | Israel | Single blind | n=62 initially evaluated  n=29 evaluated after sham treatment  n = 30 evaluated after treatment | 49-73 | Male:female = 39:20 | Isechemic or Hemorrhagic Stroke 6-36 months prior to inclusion  At least one motor dysfunction  18 years or older | Heart/lung conditions incompatible with hyperbaric oxygen therapy  Inner ear disease  Claustrophobia  Inability to sign consent  Non smoker | Hyperbaric oxygen therapy  40 sessions scheduled 5x a week  90 minutes each  100% oxygen at 2 atmospheres | Sessions for 90 minutes 5x a week | Initial neurological evalutation and secondary assessment after 2 months  Tertiary assessment at 4 months for cross group | Neurological evaluation according to NIHSS (National institute of health stroke scale)  rCBF-SPECT brain scan  Activities of daily living independence assessment (Questionaire)  EQ-5D Quality of life assessment (Questionaire) | All measures improved over the period compared to the control in the treated group, with both improving relative to their respective baselines. The controlled group had the best scores after their treatment, likely due to the increased time elapsed since the stroke.  90% of treated group had mild to significant improvement. Cross group had 36% with mild improvement and 6.2% with significant. After HBOT, cross ad 43% and 29%  Lesions began to disappear | Notes: Study used a cross evaluation, where after an inital 2 months of control, control group had two months of actual treatment  This was due to sham trials requiring added pressure without hyperbaric oxygen conditions, which would result in possibly dangerous atmospheric chamber conditions |
| 9 | Hebbian-Type Primary Motor Cortex Stimulation: A Potential Treatment of Impaired Hand Function in Chronic Stroke Patients | 2020 | USA | Double blind | n = 48 Assessed for eligibility  n = 26 Excluded in screening n=22 Tested n=2 Excluded in analysis  n = 20 Analysed | 50.6-72.6 | M:10 F:10 | Single ischemic infarction affecting M1 and/or corticospinal tract (CST) >6 months after enrollment  Motor deficit in the hand contralateral to the infarct and ability to perform the training task  No other neurological disorder affecting ability to consent or understand instructions  No contradiction to TMS or MRI  No intake of medication that could affect results  motor evoked potential (MEP) >50 μV  Absence of dementia: > 70 score on RBANS  Has ability to give informed consent | N/A | Standard Motor Training for both sham and rTMS groups: 360 auditory-cued ballsitic wrist extension movements w/ affected hand Move a cursor from its home position to a target located along the same vertical axis by extending the wrist as quickly as possible rTMS group: rTMS delivered to optimal spot for contralateral ECU muscle (supports training movement), which was determined before test  Minimum stimulus intensity to evoke MEP (motor evoked potential) of >50 μV for at least 5/10 trial = about 1% of maximum stimulator output (MSO) |  | 2-4 days before intervention (baseline) 2-4 days after intervention (posttest) 4 weeks after intervention (follow-up) | blood oxygen level dependent (BOLD) response  Jebsen Taylor Test (JTT) Secondary Test: "How Well" subtest of MAL (motor activity log) for 30 daily living activities fMRI | JTT score improved over time  MAL score improved over time rTMS increased from posttest to follow-up while sham decreased between the 2 periods    Negative correlation between hand function & contralesional M1 functional activity at baseline  Follow-up showed relation b/w hand function & m1 activity reversed relative to baseline;    Significant correlation b/w degree of improvement in hand function & change in M1 activity (b/w baseline & follow-up) for both hemipsheres of brain  (increase in hand function -> greater increase in task-related M1 activity) | Limitations: -Small sample size -Differences in performance, attention, and strategy potentially led to confounding factors in task-related fMRI |
| 10 | Robotic Assistance for Training Finger Movement Using a Hebbian Model: A Randomized Controlled Trial | 2017 | USA | Double blind | n = 48 Assessed for eligibility  n = 18 Excluded in screening  n = 30 Analysed | 44-70 | M:20 F:10 | >6 month history of unilateral stroke 18-80 years old Minimum score of 3 blocks on the Box and Blocks Test (BBT) | N/A | FINGER robootic exoskeleton used  Low vs. High Robotic Assistance applied to finger Training to play game similar to Guitar Hero Dynamically adjusted robotic assistance to aim towards 85% (for high) and 50% (for low) success rates on the game Robot only provided assistive force on movements initiated by patient w/ minimum threshold of 6-N 1 song/week played without robot assistance to measure ability to move fingers without aid | 3 1-hour training sessions per week for 3 weeks 5 songs played, twice each (1065 possible movements/session) | 2 Baseline tests (before intervention; 1 week apart from each other 2 Post-intervention tests: 1 at end of therapy (EOT), 1 follow-up after 1 month | Box and Block Test (BBT) Fugl-Meyer (FMA) ARAT Nine-Hole Peg Lateral Pinch Strength 3 Jaw Pinch Strength Motor Activity Log (How Much) Motor Activity Log (How Well) NIH Stroke Scale Beck Hopelessness Scale Geriatric Depression Scale | Motivation significantly higher for high-assistance group than low  Motivation increased over time for both groups  Baseline FMA scores acted as predictor; lower baseline -> benefit more from training)    Baseline finger proprioceptive ability acted as predictor: better propioceptive ability -> larger increase in BBT score at follow-up    Both groups generally improved for clinical & robotic measured of movement + psychological assessments    High-assistance training more effective at reducing upper extremity impairment on F-M | Limitations: - Large proportion of hemorrhagic stroke victims represented in sample - Baseline tests only 1 week apart - Protocol not designed to maximize transference of benefits of high assistance to FMA and LPG scores -Attention and motivation are factors different to separate from each other |
| 11 | Neuroplastic effects of end-effector robotic gait training for hemiparetic stroke: a randomised controlled trial Neuroplastic effects of end-effects | 2020 | Korea | Double blind | n = 75 Assessed for eligibility  n = 45 Excluded in screening n=30 Tested n=2 Withdrew  n = 28 Analysed | 42.0-64.4 | M: 23 F: 5 | Suffers from hemiplegia due to a first-ever stroke  Time after stroke onset: 3–12 months  Functional ambulation category level = 3  Korean Mini-Mental State Examination score > 24 | Has orthopaedic problems or muscle diseases impairing mobility  High risk of spontaneous fracture  Suffers from other neurological diseases | end-effector robot-assisted gait training (E-RAGT) bodyweight-supported treadmill training (BWST) E-RAGT began w/ 30% bodyweight support @ 0.8km.h & was adjusted based on individual participant  gradually reduced to 0% BW & increased to 2.0 km/h BWST began w/ same parameters as E-RAGT (30% BW, 0.8km/h) & same reduction/increase later Real-time visual feedback from pressure plates to view weight distribution and auditory cues to remain centres and maintain symmetrical movements | 30 min/day, 5 times/week, 4 weeks (20 sessions total) week 1: passive mode training  week 2 onwards: active mode    passive = track predefine trajectories + recover movement ability  active = encourage triggering robotic assistance by active effort | cortical activity-related changes were assessed at baseline (pre-test) and after 4 weeks of the intervention (post-test)  FMA, TUG, and 10MWT were assessed at baseline (pre-test), after 2 weeks of the intervention (mid-test), and after 4 weeks of the intervention (post-test) | fNIRS optical imaging system to record cortical activity-related changes in oxyHb Secondary: Lower-extremity subscale of FMA, the timed up and go test (TUG), and 10-m walk test (10MWT) | No significant Grp x Time interaction in cortical activity noted in any region  Cortical activity in SMC, SMA, PMC of affected hemisphere showed no significant Group x Time interaction    For E-RAGT, significant differences between pretest & posttest for activity of SMC, SMA, PMC at affected hemisphere  For BWST, no significant differences at any region between pre- and posttest    Fugel-Meyer (FMA) showed significant GroupxTime interaction  No sig effect of Group x Time in TUG or 10MWT results    For E-RAGT, sigificant within group differences between pre- and posttest for FMA, TUG, 10MWT  For BWST, FMA & 10MWT significantly improved after intervention | Limitiations: -small sample size -fNIRS only able to measure cortical activity but not subcortical -Procedure potentially lacked intensity and length to evoke noticeable neuroplastic change |
| 12 | High-frequency versus theta burst transcranial magnetic stimulation for the treatment of poststroke cognitive impairment in humans | 2020 | Taiwan | Double blind | n = 65 Assessed for eligibility  n = 20 Excluded in screening n=1 Withdrew before test n=44 Tested n=3 Withdrew before analysis  n = 41 Analysed | Range for whole sample unavailable iTBS: 46.03-74.23 5 Hz rTMS: 45.15-69.75 Sham: 44.23-68.23 | M:33 F:8 | left hemispheric ischemic/hemorrhagic stroke >3 months previously with cognitive impairment RBANS score below 85 no seizure history no intracranial occupying lesion no concurrent use of antidepressants or neurostimulators | unstable cardiac dysrhythmia, fever, infection, hyperglycemia, epilepsy or previous administration of tranquilizers, neurostimulators or other medication that significantly affected the cortical motor threshold metallic intracranial devices, pacemakers or other electronic devices in patient's body | Left dlPFC (F3 point) stimulated with international 10/20 electroencephalography (EEG) recording system 5 Hz rTMS and iTBS groups: 80% intensity of the resting motor threshold iTBS: 3 pulses of 50 Hz bursts repeated at 5 Hz (2-s on and 8-s off) 190 seconds (600 pulses) total 5 Hz rTMS protocol at intensity of 80% of the resting motor threshold, with 2 s trains (10 pulses) at an intertrain interval of 8 seconds, repeated every 10 seconds total of 10 minutes (600 pulses) Sham (placebo Magstim) coil was used instead for sham group <5% of the magnetic output with an audible click on discharge | 10 days of rTMS treatment, each morning from Monday to Friday for 2 consecutive weeks (10 sessions total) | Cognitive and depression status asessed before beginning of intervention and 1 day after end of intervention | Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Beck Depression Inventory (BDI) | The 5 Hz group had a significantly higher disease duration at baseline No significant differences between the 3 groups in BDI scores, nor before aand after treatment RBANS scores for 5Hz rTMS and iTBS groups poststimulation significantly increased compared to sham 5 Hz group demonstrated increased attention & delayed memory compared to sham | Limitations : -heterogeneity associated with cortical and subcortical implications -RBANS unable to assess other cognitive domains such as executive function -mechanism for rTMS is still mostly unknown |
| 13 | Comparison of Neuroplastic Responses to Cathodal Transcranial Direct Current Stimulation and Continuous Theta Burst Stimulation in Subacute Stroke | 2018 | Switzerland | Double blind | n = 184 tested for eligibility  n = 41 included in study | 28-85 | Male:Female = 18:9 | Ischemic or Hemorrhagic stroke  ≤10 weeks after stroke  Unilateral lesion in the territory of the middle cerebral artery  First-ever appearance of upper extremity motor Impairment based on the Fugl-Meyer upper extremity scale | epileptic seizures  presence of metallic objects in the brain  skull breach after craniectomy  presence of implants or neural stimulators  pregnancy, sleep deprivation, recent traumatic brain  injury, delirium or disturbed vigilance,  inability to participate in 1-hour treatment sessions  severe language comprehension deficits  new stroke lesions during rehabilitation  medical complications | neuronavigated cTBS - One application consisted of a continuous train of 267 bursts, each composed of 3 pulses applied at 30Hz, repeated at interburst intervals of 167 milliseconds. The train lasted approximately 30 seconds and consisted of 600 stimuli.  cathodal tDCS - 25 minutes at an intensity of 1mA  sham transcranial magnetic stimulation/sham tDCS - current was ramped up for 30 seconds and then slowly tapered down to zero | Each subject completed 9 stimulation  sessions over 3 weeks, combined  with physical therapy | Brain function was assessed with directed  and nondirected functional connectivity based  on high-density electroencephalography before  and after stimulation sessions | Fugl-Meyer Assessment score,  Box and Block test score,  9-Hole Peg Test score, and Jamar dynamometer | Only cTBS was able to reduce transcallosal influences from the contralesional to the ipsilesional M1 during rest  tDCS enhanced perilesional beta-band oscillation coherence compared with cTBS and sham groups  enhancement of perilesional beta-band connectivity through tDCS might have more robust clinical gains if started within the first 4 weeks after stroke. | absence of significant clinical differences between the 3 groups of subjects involved in study could be caused by the small sample size.    cannot extrapolate the results presented here to protocols applied to the affected hemisphere. cTBS and tDCS may show comparable effects in this case. Moreover, excitatory protocols applied to the affected hemisphere may be less time sensitive. |
| 14 | Low-Frequency Repetitive Transcranial Magnetic Stimulation Over Contralesional Motor Cortex for Motor Recovery in Subacute Ischemic Stroke: A Randomized Sham-Controlled Trial | 2020 | South Korea | Double blind | n=79 provided consent during screening  n =2 declined to participate  n = 4 withdrew consent  n = 73 analyzed | Real rTMS (n = 36)  61.2 ± 11.2  Sham rTMS (n = 37)  62.9 ± 13.1 | Real rTMS (n = 36)  M:F = 21:15  Sham rTMS (n = 37)  M:F = 24:13 | displayed unilateral upper limb hemiparesis in  Brunnstrom hand stage rating of 3 to 5 within 90 days after first-ever ischemic stroke onset confirmed by magnetic resonance imaging (MRI).    They were aged between 20 and 80 years | hemorrhagic or recurrent stroke  previous history of traumatic brain injury  seizure or cerebrovascular surgery  need for intensive care due to severe complications  of stroke  metallic materials in the body,  (eg, pacemakers, cochlear implants, aneurysm clips)  pregnant or lactating women  likely to become pregnant but did not agree to  appropriate contraception during the trial  skin lesions around the contralesional M1 which  interfered with rTMS, or those who could not  regularly receive occupational or physical therapy. | 1 Hz rTMS over the contralesional M1  sham rTMS | applied for 30 minutes per day  over 10 days | assessed at baseline (T0),  immediately after the end  of treatment (EOT, T1),  and 1 month after EOT (T2) | change in the Box and Block Test (BBT) results  between baseline and immediately after EOT  upper extremity FMA score;  Finger Tapping Test (FTT);  hand grip, pinch grip, lateral  prehension, and three jaw chuck strength;  Brunnstrom hand and arm stage ratings;  modified Ashworth Scale (MAS) in  the elbow, wrist, and finger flexors;  Korean version of Modified Barthel Index (K-MBI) | no significant differences in changes in any outcomes between real and sham rTMS    BBT from baseline to 1 month after EOT in PP set revealed a trend for greater improvement for real rTMS than for sham rTMS (16.9 ± 9.7 real vs 11.9 ± 9.7 sham; P = .038) but this pattern did not remain statistically significant following Bonferroni correction | orticospinal tract integrity was not objectively measured using  single-pulse TMS or brain imaging. The degree of corticospinal tract integrity  is a strong predictor of motor recovery    did not measure the changes in cortical activation pattern or neurophysiological parameters using functional neuroimaging or paired-pulse TMS in all patients    the possible differences in rTMS effect on motor recovery according to hemispheric dominance was not considered    most of the outcomes in this study were focused on assessing the hand function. Therefore, it is possible that the effects of rTMS on proximal arm recovery were not captured well    medications which can promote motor recovery after stroke were not limited during this study    various rehabilitation modalities could not be exactly counterbalanced between the groups from EOT to 1-month follow-up |
| 15 | Transcranial electrostimulation with special waveforms enhances upper-limb motor function in patients with chronic stroke: a pilot randomized controlled trial | 2021 | Taiwan | Single blind | n = 36 Assessed for eligibility  n = 12 excluded  n = 24 analyzed | Real NIBS (N = 12)  62.08 ± 15.58  Sham NIBS (N = 12)  65.92 ± 13.98 | Real NIBS (N = 12)  M:F = 9:3  Sham NIBS (N = 12)  M:F = 7:5 | patients with ischemic or hemorrhagic  chronic stroke (within 6 months to 5 years after onset);  aged ≥ 20 years;  unilateral cerebral stroke with hemiplegia and Brunnstrom stage IV or V;  adequate understanding of verbal/written information and physically able to complete the motor learning of functional tasks with the affected hand; | lower motor neuron impairment;  unstable autonomic nervous system;  extremely sensitive to electrical stimulation and could not tolerate it;  contractures in the upper extremity or limitations of joint motion;  severe spasticity;  myositis ossificans;  a history of arrhythmia;  a medical electronic device implant, such as a pacemaker;  decubitus or scalp wounds;  metal head or neck implants;  severe cognitive dysfunction or active psychiatric diseases, such as schizophrenia or dissociative identity disorder;  history of seizures or organic brain disease;  severe traumatic brain injury;  drug or alcohol abuse;  a malignant tumor or an autoimmune rheumatic disease, such as systemic lupus erythematosus, rheumatoid arthritis, or ankylosing spondylitis; | real NIBS which included conventional rehabilitation (CR) combined with  real-tDCS + iTBS output; 1.5-mA intensity was superposed on continuous 1-mA DC    sham NIBS with sham-tDCS + iTBS output (the sham NIBS group) stimulation intensity current was ramped up to 1 mA and then the current was ramped down to 0 mA | 18 sessions of a 1-h CR program  (i.e., 3 days a week for 6 weeks),  where a 20-min NIBS current was  simultaneously applied at  the beginning of the 1 h of CR in all sessions | week before treatment  initiation (baseline);    functional outcomes were measured at the baseline, immediately after, and 6 weeks after 18 therapeutic sessions (post-treatment) | FMA-UE was performed (score ranges 0 ~ 66)  to assess upper-limb motor recovery;    Jebsen-taylor hand function test (JTT)    Finger-to-nose test (FNT) | FMA-UE - significant time effect with an  increase in mean FMA-UE scores in both the sham NIBS group  (from 45.17 ± 17.18 at the baseline to 52.17 ± 15.03 post-stimulation; p < 0.001)  and the real NIBS group (from 37.50 ± 20.54 at the  baseline to 48.33 ± 16.55 post-stimulation; p < 0.001);    JTT and FNT Times Increased in Real NIBS group | did not include conventional tDCS or iTBS stimulation as a comparison group in study;    study was single-blinded due to characteristics of the tDCS device. This could potentially have caused bias when conducting the sessions;    sample size was small, so applications in large population are required in the future    study tested electrostimulation only on chronic stroke patients with upper-limb impairment (Brunnstrom stage IV or V)    other neurological conditions, like Alzheimer’s and Parkinson’s disease, will be tested in the future for the effect of electrostimulation on the brain for improvements in cognition, memory, and functional activity status to develop smart electrostimulation devices for use in clinical rehabilitation |
| 16 | Transcranial Direct Current Stimulation Enhances Motor Skill Learning but Not Generalization in Chronic Stroke | 2018 | USA & Germany | double-blinded | n =272 Assessed  n =56 proceeded  n =6 withdrew  n - 50 Analyzed | SHAM tDCS(N=18)  61.6±3  Real tDCS (N=18)  61.9±3  NO TRAINING/  NO tDCS (N = 14)  64.7±2 | SHAM tDCS(N=18)  M/F = 67/33%  Real tDCS (N=18)  M/F = 83/17%  NO TRAINING/  NO tDCS (N = 14)  M/F = 57/43% | age 18–80 years;  unilateral, first ever ischemic stroke more than 3 months before study enrollment;  mild to moderate hemiparesis with residual hand function sufficient for task performance;  clear hand preference as assessed by the Edinburgh Handedness Inventory;  sufficient cognitive function to comply with study requirements; | N/A | (40µA/cm2) real or shame tCDS for 20 minutes per day with the anode targeting the primary motor cortex (M1) of the affected hemisphere | five consecutive days and  were then subjected to 5 follow-up visits | Every day for 10 days starting from first day of tCDS | practiced a modified version  of the sequential visual isometric  pinch force task (SVIPT) for approximately  45 min per day | Both training groups show increased accuracy, effect was catalyzed by tDCS  (a reduction in no. of errors is indicated by positive values), on all days, while the  no-training/no-tDCS group shows less accuracy    Total learning was significantly enhanced by tDCS    Compared to sham tDCS, patients showed more online learning and less offline learning when stimulated with real tDCS | unable to infer which stimulated cortical areas may contribute most to learning    required that patients have sufficient hand function to execute the SVIPT, it is unclear how results would translate to more severely affected patients    long-lasting generalization to untrained upper extremity function due to training, but no additional benefit provided by tDCS, could include a more impaired patient cohort and more multifaceted generalization measures to comprehensively gauge stimulation effects in the clinical context |