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# Means of Effectiveness of Treatments Inducing Neuroplasticity for Rehabilitation After Stroke

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## ABSTRACT

Two main causes of stroke in a person are recognized as an ischemic stroke or a hemorrhagic stroke. The former is caused by a blocked brain artery, whereas the latter is due to a bursting of a blood vessel (Mayo Clinic, n.d.). As it stands, there are currently a variety of treatments used on individuals who undergo a stroke. Many of these treatments consist of inducing a "rewiring" in the brain to reduce, and sometimes rid the individual of the effects of a stroke. This phenomenon is commonly recognized as neuroplasticity. In order to induce neuroplasticity, the treatments in question are typically rehabilitation activities. It is important to understand that a stroke causes damage to the brain due to interrupted blood flow. Through increasing neuroplasticity in one's brain, it is possible to make cellular as well as neuronal connections in the parts of the brain damaged during the course of the stroke. In this paper, the treatments discussed will be evaluated on their efficiency, ease of access, and how well they achieve their purpose. These treatments represent 4 different facets of intervention: neuromodulatory therapy, physical therapy, conventional therapy, and language therapy.

## Introduction

According to the Center for Disease Control, someone in the United States has a stroke every 40 seconds. About every 4 minutes, someone dies of a stroke (Center for Disease Control, n.d.). Given how commonly individuals can be affected by strokes, finding the right way to treat affected individuals is vital. With the number of varying treatments that medicine currently has to offer, it is necessary to be able to find the most effective solution to such an issue. The methods of treatment this review will look into consist of ways which utilize neuroplasticity to help victims recover, such as transcranial electric stimulation, aerobic exercise, robot-assisted training, the use of music, and cell therapy.

## Treatments

### Transcranial Electric Brain Stimulation

Brain stimulation treatment is typically recognized as non-invasive (when in the form of TMS/tDCS) and is usually performed via electric stimulation. This form of treatment usually helps the most with symptoms that may occur after the stroke, such as aphasia and motor functionality. Hordacre et al. (2018) use functional magnetic resonance imaging (fMRI) in their study to measure results of brain growth. (Park et al., 2011; Quinlan et al., 2015). Both fMRIs and electroencephalograms (EEGs) are used to study network connection as well as corticospinal excitability, which both can be used to measure induced neuroplasticity (Wu, Srinivasan, Kaur, & Cramer, 2014). Certain test subjects were given anodal tDCS, whereas others were given sham tDCS. The group given the latter was used as a control group, whereas the former was experimental. Again, the end goal of the study was to research whether or not the anodal tDCS resulted in increased network connectivity as well as corticospinal excitability. Anodal tDCS allows for the depolarization of brain cells (Nunomura et al., 2020). Those who were tested with anodal tDCS were delivered 1 mA for approximately 20 minutes with a 30 seconds ramp up as well as a ramp down, whereas sham tDCS was given a 30-second ramp up to 1 mA followed by an immediate fall to 0 mA with no further electrical stimulation. Different electrodes gave off different bands, with researchers concluding that alpha waves were the most effective in accordance with the anodal tDCS.

It is important to note that "high intersubject variability" was a leading factor behind why less than 50% of the subjects ended up with an increase in corticospinal excitability, as well as why there was no viewable group difference in the subjects' responses to either anodal or sham tDCS. This is not uncommon, as the same issue has occurred in previous studies such as this one. The authors note that this, therefore, reduces the ability of this treatment to be used in a commonly therapeutic manner.

Post-experimental evidence, however, did point to increased network connectivity which was found to have an association with brain plasticity. fMRI scans indicated increased connectivity in the lesioned areas of the brain, which had affected the motor function of chronic stroke patients (Park et al., 2011; Quinlan et al., 2015). Whereas in EEG scans, areas of connectivity indicated the ability for better navigation through a motor learning task (Wu et al., 2014). However, it should be noted that EEGs consist of limitations caused by limited spatial resolution as well as volume conduction affecting signals recorded at an individual's scalp. (Bastos & Schoffelen, 2016). The authors noted, however, that they believed this form of intervention to be most efficient on only a subset of chronic ischemic stroke victims. This small sample did not reach statistically significant results.

## Aerobic Exercise

Aerobic exercise is recognized as modern therapy. A very common form of treatment is known as "conventional rehabilitation", e.g., physical therapy (Su & Xu, 2020). This form of treatment has been shown to be most effective when intensive, and consistent over long periods of time. (Kelly, Brady, & Enderby, 2010; Langhorne, Bernhardt, Kwakkel, 2011).

Linder et al. (2019) suggested that intensive physical training will serve as a factor that will facilitate neuroplasticity and therefore allow for more efficient motor recovery after a stroke. For their measure of neuroplasticity, the authors relied on the increase of cortico-spinal excitability in the individual as well as the increase of brain-derived neurotrophic factor (BDNF), a neurotrophin which, when detected, indicates motor recovery. They noted that this is a measurement standard that has been used in previous studies regarding the same subject to test brain plasticity. In their testing, the authors have 3 groups of subjects. Individuals who underwent forced exercise (FE) alongside repetitive task practice (RTP), individuals who underwent voluntary exercise (VE) with RTP, and lastly, the third group underwent stroke education sessions with RTP. The last group acted as a control whereas differences between all 3 groups were used to measure which allowed for neuroplasticity to occur the quickest. One of the questions answered by the authors is exactly what conditions of exercise allow for the proper outcome of allowing the most efficient motor recovery after the stroke has occurred. They used aerobic intensity, rate intensity, power intensity, as well as the length of the session for both groups to measure this. All of these variables, with the exception of rate intensity, were about matched between both groups, with the FE group peddling about 22% faster than the VE group. This variability is accounted for, however when one takes into consideration that the FE group was working at a higher intensity training, therefore causing this increase in pedaling speed (Linder et al., 2019).

Two tests were conducted to retrieve results. These tests consisted of the Fugl-Meyer Assessment (FMA) and the Wolf Motor Function Test (WFMT), which determine an individual's general movement ability as well as their ability to complete both timed and strength-related fine motor skill tasks, respectively. In regards to the FMA, data analysis shows that all 3 groups scored high, with the FE + RTP group scoring the highest. When the WFMT is analyzed, all 3 groups also were shown to have higher motor function, with the FE + RTP group specifically showing an increase in grip strength as well. The FE + RTP group overall showed the most significant improvement as compared to any other group tested. It is important to note that statistical significance was not found among the groups, and furthermore that the variables such as BDNF and corticospinal excitability were not measured and instead believed to have taken place given the results. Regardless, one can assume that neuroplasticity did take place to a degree, given the state of the FE + RTP group at the end of the study.

## Robot-Assisted Training

Robo-assisted training and therapy typically help most with limb training in individuals who have lost some motor function after having a stroke. Most training consists of everyday life activities in hopes of training muscle strength alongside arm and leg functionality. In a study done by Calabro et al. (2018), the authors posed a possibly better alternative to traditional overground gait training (OGT) therapy used on stroke victims. In this study, individuals were fitted with an Ekso™ wearable exoskeleton, which the authors hope could possibly result in increased gait performance as compared to orthodox OGT treatments. The authors used network connectivity, specifically frontoparietal effective connectivity via EEG, as well as corticospinal excitability to measure neuroplasticity throughout the course of this experiment. The experiment consisted of 2 groups of 20 people, each randomly assigned into said groups. Group number one consisted of 20 individuals who would undergo OGT training, whereas group two had the remaining subjects undergo Ekso™ gait training (EGT). Both groups would have physiotherapy training consisting of 60-minute sessions five times a week for 8 straight weeks.

**Figure 1.** The Ekso™ wearable exoskeleton used in the study. As can be seen, the exoskeleton is properly fitted onto the individual, which is then attached to a rail tether on the ceiling. (Calabró et al., 2018). CC BY 4.0.

Interestingly, transcranial magnetic stimulation makes a return, as in this study, it was used to measure corticospinal excitability. Both groups of subjects were tested on a 10-meter walk test (10MWT), a Rivermead Mobility Index (RMI), and a timed up-and-go test (TUG) both before and after treatments were applied. Subjects who underwent EGT, in comparison to OGT subjects, took less time on the 10MWT and the TUG, and they also had a higher score on the RMI test. In conclusion, the authors reported statistically significant values in their corticospinal excitability and frontoparietal effective connectivity measurements, which provided evidence that EGT induced neuroplasticity in these subjects.

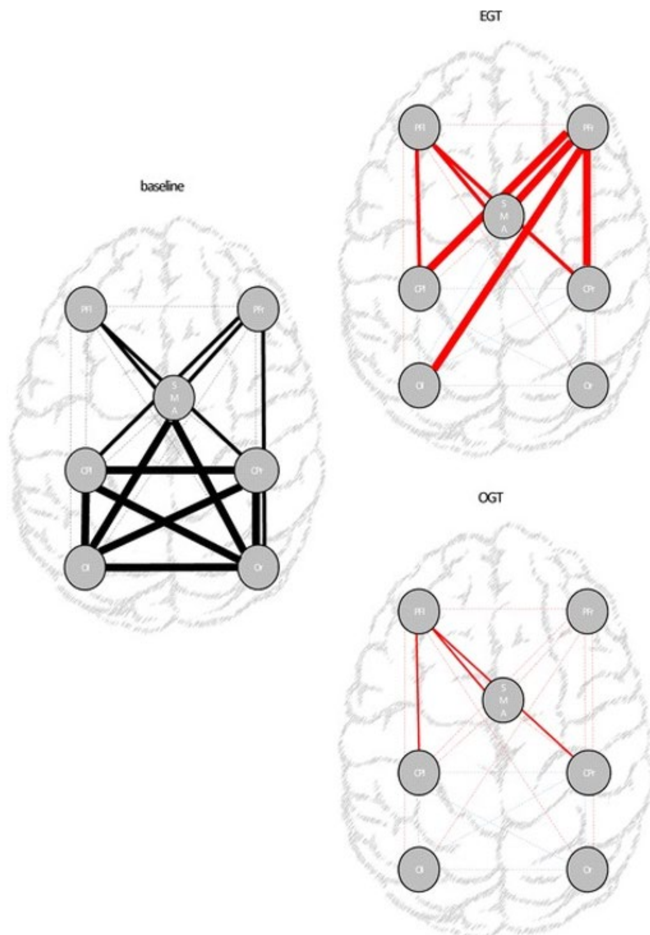


**Figure 2.** Shown above are the different connectivity paths for EGT and OGT groups, as well as baseline connectivity. The color red indicates an increase in path connectivity, whereas blue is a decrease (in regards to after training in comparison to before training). Line thickness indicates different things. Thick: after/before training effects were able to be analyzed only after EGT. Medium: effects were greater following EGT as compared to OGT. Thin: effects were equal in both groups. (Calabró et al., 2018). CC BY 4.0.

There were no issues during the course of the study, with the exception that minor skin erythemas occurred on the legs of 7 patients using the exoskeleton suit. In regards to limitations, no long-term follow-up or evaluation ever occurred. Though results were expected to last.

## Music

One particularly interesting study by Sihvonen et al. (2020) investigated the use of music for the possible rehabilitation of individuals. Vocal Music can be recognized as another form of conventional rehabilitation, in this case, specifically language therapy.

For this study, the authors use music as environmental enrichment (EE) to drive the induction of neuroplasticity. They note that environmental enrichment drives plasticity, neurotrophin production, as well as neurogenesis (Livingston-Thomas et al., 2016). Neuroplasticity was directly measured via brain connectivity viewable by fMRI scans as well as voxel-based morphometry scans (VBM). Subjects selected for the experiment were stroke patients chosen from randomized controlled trials previously performed and were given different forms of audio stimuli. Group

1 was given vocal music with sung lyrics (VMG), Group 2 instrumental music with no sung lyrics (IMG), and Group 3 narrated audiobooks, without music of any sort (ABG). Patients were made to listen to the audio stimuli for a minimum of an hour a day for 2 months straight, after which they would then have a follow-up with a professional music therapist.

Subjects were evaluated based on an assessment battery which consisted of three subjects: verbal memory, language skills, and focused attention. Evaluation occurred multiple times, such as at less than three weeks (T0), 3 months (T1), and 6 months (T2). Data analysis shows that significant differences were found in comparison to time groups such as T0 to T1 and T0 to T2 for the VMG group compared to the 2 other groups. These differences consisted of the fact that VMG had the highest improvement rate for verbal memory when compared to IMG (timetable of T0-T1) and was higher than ABG in timetable T0-T2. Significant data was also found when comparing VMG to ABG in regard to language recovery. Overall, VMG seemed to show the most drastic improvement. This makes sense when one takes into account the fact that music, in the first place, serves as a tool these individuals can use for language recall, given the fact that they are able to make connections with lyrics within the music. In regards to neuroplasticity, grey matter volume (GMV) increased more in VMG as compared to other groups. Concerning aphasics, there was also a significant GMV increase in the IMG group as compared to the ABG group. It is also important to note that because the study was a pooled analysis of two randomized controlled trials, which allows for possible self-selection bias. The authors, however, counter this by stating that both trials were conducted very similarly and that measurements were covaried. Therefore, the authors feel that there was no significant bias within the experiment.

## Discussion

In order to evaluate which treatment is most efficient, limitations and possible setbacks are two of the most important variables that must be taken into account. Studies that used EEGs to measure patient neuroplasticity suffer from the fact that EEGs themselves have, as earlier mentioned, poor spatial resolution as well as signal reading mishaps. A common point for all of these forms of treatment is that they are all non-invasive. None of these treatments hurt the individual during the administration process of the treatments to the individuals.

However, certain studies, such as the forced aerobic exercise experiment, falter in that they did not specifically use any form of tool to attempt to measure neuroplasticity levels despite noticing improvement in individuals after the experiment had been completed. Both robot-assisted training as well as the use of music had mostly significant figures when listing their data as well as induced neuroplasticity (the former used brain connectivity whereas the latter makes use of gray matter volume increase within the brain).

Other limitations consist of technical and methodological issues. Technical issues stem from the fact that certain machinery may limit measurements to a degree. This is apparent in EEG measurements. For example, in the case of the neuromodulatory treatment, transcranial electric brain stimulation, the EEGs used to measure brain connectivity, and corticospinal excitability may suffer from poor spatial resolution. Other factors in this study, such as intersubject variability, may also affect results. The other type of limitation would consist of human error/mistake. In the case of the study used when reviewing how music intervention may assist stroke patients, the authors, as earlier mentioned, noted that the study might suffer from self-select bias. Though, the reasoning used by the authors works to discount bias in the experiment. Regardless, both tDCS and Ekso™ gait training did not suffer from this issue. Though aerobic exercise didn't suffer from bias either, they did make what one would assume to be a methodological error in that they did not measure neuroplasticity specifically and instead hypothesized that it occurred based on the experimental results shown in patients.

Perhaps one of the most important things concerns the ease of translation of interventions into clinical use. Hordacre and co.'s tDCS study, for example, suffers from this issue. Because of intersubject variability, which causes trouble in the visualization of group differences, use in clinical use becomes a bit of an issue. In the case of robot-assisted training, gait training is commonly used in a clinical setting. The same goes for language training. The proposed idea of using music to help rehabilitate stroke patients, as well as the use of gait training, therefore, would have no problem being paired together and implemented to be used by those who have suffered a stroke.

Lastly, one more factor that must be evaluated is the ease of access and the variety of people each treatment may help. Perhaps one of the biggest side effects of stroke is language and movement reduction. Thankfully, the intervention methods listed above are meant to assist with these issues.

## Conclusion

In summation, the use of music, surprisingly enough, seemed to invoke the largest change in individuals as compared to other forms of treatments discussed. The music study, recently conducted by Sihonen et al. (2020) properly measured neuroplasticity through the use of an fMRI, which specifically measured GMV and functional connectivity.

Results showed an increase in language recovery in aphasic patients as well as verbal memory for those who listened to the music with sung lyrics. Given how easy music would be to implement as a form of intervention for patients in a clinical setting, as well as its ease of use in *any* setting, including the fact that results were so impressive (reference gray matter volume expansion), it is not difficult to understand why this treatment would be recognized as one of the more efficient ways to help those who have unfortunately suffered symptoms from a stroke. Pairing this form of intervention with other easily accessible forms of treatment, like aerobic exercise or robot-assisted training, may serve to greatly benefit those who suffer a combination of deficiency in both motor and language skills.

## Limitations

Understandably one may point out that the differences between the experiences that patients endure after a stroke differ too widely in order to make a basis of an argument on which treatment would be most effective, given that the forms of intervention in this review deal with two different things: motor recovery and language recovery (depending on the treatment). However, recent single-case studies performed actually show that language changes coincide with motor function repair (Primaßin et al., 2015). A brief report was done on the same phenomenon in hemiparesis victims (Harnish et al., 2014). It should be noted that hemiparesis is a possible side effect a stroke can leave on an individual. These circumstances open room for more research to be done in regard to the simultaneous recovery of different parts of the brain should multiple areas be affected by a stroke.

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