Physiotherapy interventions for enhancing neuroplasticity in people with spinal cord injuries: A systematic review of randomized control trials

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ABSTRACT

A systematic review of randomized control trials was conducted to provide an overview of the effectiveness of physiotherapy interventions for enhancing neuroplasticity and by extension functional recovery in people with SCI.

The appropriate MESH keywords were used in September of 2022 to search the global databases: PubMed, Science Direct, Cochrane and Scopus. In the review, only randomized controlled trials (RCTs) were included, which met the inclusion and exclusion criteria. The RCTs that were included in this review evaluate the effect of different physiotherapy interventions on neuroplasticity in people with spinal cord injuries. All studies were assessed for risk of bias using the Pedro scale.

In our study, we included 6 randomized control trials. Interventions such as massed practice with somatosensory stimulation, exercise with corticospinal neural stimulation, endurance training, intermittent hypoxia (IH) combined with Body weight supported treadmill training and paired transcranial direct current stimulation (tDCS) with Locomotor training with a robot-assisted gait orthosis (LT-RGO) were shown to enhance neuroplasticity and induce functional recovery in people with SCI. Therefore, further research needs to be done.

Keywords: Spinal Cord Injuries, Physical Therapy Modalities, Neuronal Plasticity

Introduction

Spinal Cord Injuries are serious medical conditions that often lead to severe disability. In spinal cord injuries, the nerve axons of the spinal cord are disrupted and this leads to loss of sensory and motor function [1]. The most frequent occurrence is the result of major trauma. Spinal cord injuries, depending on the severity of the trauma, are classified as complete or incomplete.

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This classification is based on whether there is some sensory and/or motor function below the injured level [2]. It is important to note that a clinically complete SCI is most of the times, not a pathological complete cut of the spinal cord and there are remaining neural pathways.

A certain degree of recovery for incomplete and even complete SCI can be achieved through physical rehabilitation. The amount and extent of recovery depends on multiple factors, including the level and extent of injury, post-injury medical care, and rehabilitative interventions. Plasticity as the Merriam-Webster's Medical Dictionary defines is "the capacity for continuous alteration of the neural pathways and synapses of the living brain and the nervous system in response to experience 5or injury''. It has been reported that there is a reorganization of cortical maps after spinal cord injury that occurs spontaneously [3]. Green et others showed that patients eventually regaining function after SCI, are initially presented with a posterior shift in cortical motor potential [4] The nervous system has the ability to enlarge cortical territories that are controlling functioning body parts and to invade cortical areas that have lost the peripherical target [5]. Also, another ability of the nervous system is to strengthen and weaken synapses in response to input. These synaptic changes are essential for learning, memory, and motor output under normal and pathological conditions. Decades of research revealed that the injured central nervous system retains the capacity for neuroplasticity even during the chronic phase of injury [3].

Plasticity is an incredible ability of the nervous system, giving it the capacity to learn and recover after trauma. Without the guidance of rehabilitation though, it yields limited functional improvements following SCI [6]. Existing physical therapy interventions for SCI mostly focus on minimizing secondary complications and compensating for lost function instead of targeting enhancing neuroplasticity and restoring pre-injury abilities [7]. Further research is urgently needed to be done in new physical therapy interventions approaches for facilitating physical function beyond conventional therapies and to promote quality of life among people with SCI [8].

The purpose of this systematic review was to provide an overview of the effectiveness of physiotherapy interventions for enhancing neuroplasticity and by extension, functional recovery in people with SCI.

We conducted a search of the literature using the key words: "Spinal Cord Injuries", "Physical Therapy Modalities", "Neuronal Plasticity" on September 2022. We used the following search strategies using Mesh Terms: (i) on PubMed and Cochrane: (("Spinal Cord Injuries" [Mesh]) AND ("Physical Therapy Modalities" [Mesh]) AND ("Neuronal Plasticity" [Mesh]) and (ii) on Science Direct and Scopus: ("Spinal Cord Injuries" OR "Cord Trauma" OR "Spinal Cord Injury") AND ("Physical Therapy Modalities" OR "Physiotherapy" OR "Physical Therapy") AND ("Neuronal Plasticity" OR "Neuroplasticity"). We included studies of people with Spinal Cord Injuries, no matter if the injury was acute or chronic, traumatic or non-traumatic and whether the classification of the injury was complete or incomplete. Only randomized control trials that were published in the last 20 years were included in this review. All the studies that were included were in English. All animal studies were excluded.

Risk of Bias: All studies were assessed for risk of bias using the Pedro Scale. The Pedro scale was developed in 1999 to evaluate the risk of bias and completeness of statistical reporting and is now commonly used in systematic reviews [9]. The Pedro Scale evaluates 11 items: inclusion criteria and source, random allocation, concealed allocation, similarity at baseline, subject blinding, therapist blinding, assessor blinding, completeness of follow up, intention-to-treat analysis, between-group statistical comparisons, and point measures and variability. Each item is rated as "yes" or "no," and the total Pedro score is the number of items met (excluding criteria 1) (Maher,, Sherrington, Herbert, & Moseley, 2003). Eight items evaluate risk of bias and two completeness of statistical reporting. Depending on the Pedro score the study is consider to have poor (<3), fair (4-5), good (6-8) or excellent (8-10) methodological quality. Pedro scoring for each study is presented on **Figure 3.**

Results

We conducted our search on September 2022 on PubMed, Cochrane, Scopus and Science Direct and retrieved 649 studies. By applying the inclusion and exclusions criteria and by reading the full text and excluding duplicate publications, we identified 25 clinical trials. From the 25 clinical trials only 6 of them were randomized control trials that were evaluating physical therapy effects on neuroplasticity in people with spinal cord injuries and were included in our systematic review [11-16]. The studies are presented in **Figure 2.**

The evaluation of Risk of bias is presented on Figure 3. As is shown on the table only 2 studies were considered high quality and scored 10/10[16][15]. Three of the six studies were considered of good methodological quality by scoring 6/10 and 7/10 [1-13]. Only the study of Khan et al, 2016 was considered of fair methodological quality with score 5/10 [14].

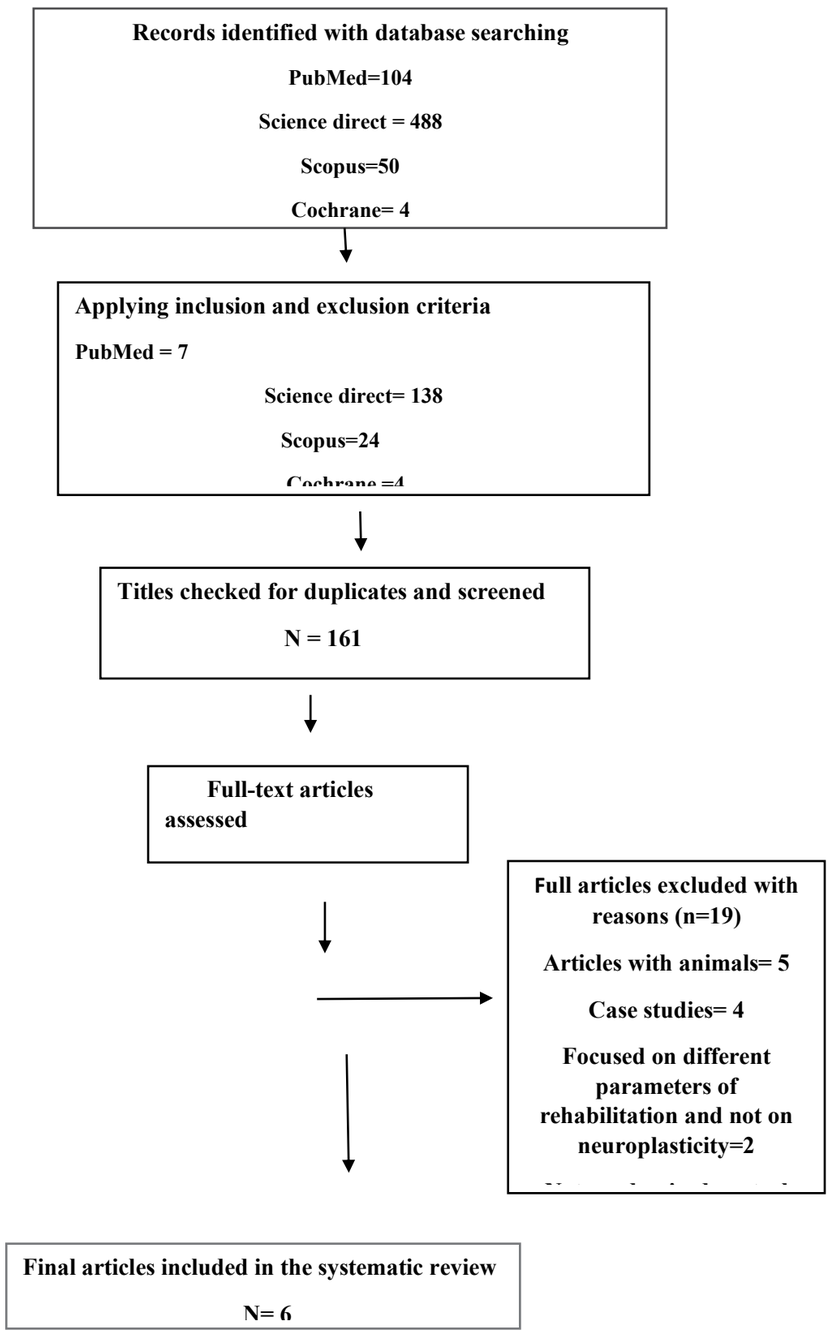
The limitations of the included studies were the sample size, and in most of them, as with all exercise interventions, the fact that participants cannot be blinded to the intervention. In all of the studies, the sample size was very small, with the biggest sample size being only 38 people with SCI, in the research of Hang Jin Jo et al, 2020. Further research needs to be done with a larger sample size. Also, the fact that in most cases, reports of participants, therapists and evaluators were not blinded could have created bias.

Discussion

In both randomized Control Trials of Beekhuizen et al, in 2005 and 2008, their purpose was to evaluate the effect of massed practice with somatosensory stimulation on upper extremity hand function and cortical excitability in people with cervical spinal cord injuries [11,12]. In the study of Beekhuizen et al, 2008 the comparison groups were 4 massed practice group (MP), Massed Practice and Somatosensory stimulation group (MP+SS), Somatosensory Stimulation Group and Control group, contrary to Beekhuizen et al, 2005 when there were only 2 groups, MP and MP+SS. In both studies they hypothesized that the combined intervention MP and SS, would result in greater changes in the previously mentioned outcomes. Both studied used as outcome measures the Jebsen-Taylor Hand Function Test (JTHFT) scores, the Wolf Motor Function Test (WMFT) timed task scores, (3) the maximal pinch grip force, (4) the Semmes-Weinstein monofilament sensory testing, and (5) the intensity of the cortical stimulation required to evoke a motor threshold response (50-100 μV) in thenar muscles. The results of both studies indicated that practice of functional tasks combined with augmented afferent input was associated with the greatest change in hand and upper-extremity function, pinch strength, and sensory scores. MP+SS did not differ significantly from SS in several of the outcome measures though. The fact that there were significant improvements in the group receiving somatosensory stimulation alone suggests that afferent input may be a powerful tool in promoting neural plasticity. No measurable changes appeared in cortical excitability on the study of Beekhuizen et al, 2005 but this was probably due to the time of intervention, the small sample and the fact that they evaluated the same location as the pretesting measurement. This preliminary study did not find significant changes in cortical excitability after MP+SS or MP training, and the lack of significant results may be due to the low power (54.3%) to detect differences between the groups in this study. On the study of Beekhuizen et al, 2008 where the cortical excitability was evaluated via MEPs threshold, they identified a significant between-groups difference (F=19.06, p=.001) for the MEP threshold data, with the regression model explaining 78.5% of the variation in the data. All else being equal, both the MP+SS group and the MP group differed significantly from the control group (t=-4.28, p=0.001, t=-4.25, p=0.001, respectively).

In the study of Han Ji jo et al, 2020 the purpose was to investigate the effect of paired corticospinal-motor neuronal stimulation (PCMS) combined with exercise on augmenting changes in corticospinal transmission and motor output [13]. Thirty-five people with chronic incomplete spinal cord injury randomly assigned to three groups, exercise with PCMS, exercise with sham-PCMS and PCMS only. The primary outcome measures that were used were the Maximal voluntary contraction (MVC) and Motor evoked potentials (MEPs) of each of the muscle tested. MEP size increased after 10 sessions of PCMS + exercise and PMCS (64.6±65.0%, p<0.01). MVC increased after 10 sessions of PCMS + exercise (48.0±54.9%, p< 0.01) and PCMS (42.8±25.7%, p< 0.001) but not after sham-PCMS + exercise (1.3±13.5%, p=0.7) compared with baseline. The time to perform functional tests decreased in all groups: PCMS + exercise (by 24.4 ± 18.6%, p<0.05), PCMS (by 19.5 ± 9.1%,

Table. 1 Flowchart



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p< 0.05) and sham-PCMS + exercise (by 17.4±20.1%, p<0.05). Six months later the results persist only in PCMS + exercise group (p<0.05). The findings suggest that PCMS is an effective strategy to facilitate exercise-mediated recovery can help maintain the effects gained in humans with SCI.

In the study of Khan et al,2016 the purpose was to determine whether individuals with SCI showed training-specific spinal plasticity in response to 2 different forms of exercises, endurance training and precision training [14]. In the study, 20 people with SCI participated, between C1-L1 neurological levels. They were randomly assigned to 2 groups and trained according to one type of exercise for two months, followed by two months of rest, and then crossed over to the other exercise regimen for another two months of trainings. As primary outcome measures, they used clonus and cutaneomuscular reflex induced by stimulating the posterior tibial nerve (PTN). The results showed that only Endurance Training induced a significant enhancement of the inhibition in the SOL CMR. Neither form of training changed clonus in a systematic way. The results suggest that intensive training or walking reduce the abnormal reflex excitability seen after SCI and this enhanced inhibition is concurrent with training-induced strengthening of corticospinal input to the motoneurons / interneurons.

The purpose of the study of Navarrete-Opazo et al, 2016 was to compare the effect of a 4-week protocol of intermittent hypoxia (IH) combined with BWSTT (experimental group) versus continuous Normoxia with BWSTT (control group) on eliciting plasticity in the spinal cord and strengthening spared synaptic pathways [15]. The plasticity is expressed as respiratory and somatic functional recovery, that's why they used, as the primary outcome measure, the 10-m walk test (10MWT). As secondary outcome measures, they used the 6-min walk test (6MWT) and the timed up and go (TUG) test. At the study, 35 people with chronic ASIA C and D incomplete SCI participated. The IH group had a greater walking speed than the control group, expressed as a decrease in 10MWT time versus baseline in 5 days (IH: -10.2-3.0 vs. Nx: -1.8-1.7 sec, p = 0.006). In week 2 (IH: -15.5-4.8 vs. Nx: -3.7-3.3 sec, p = 0.04) and week 3 (IH: -17.1 – 5.3 vs. Nx: -7.1 – 2.8 sec, p = 0.03). Not a significant difference in TUG time. There was a greater walking endurance in the IH group compared to the control group on day 5 (IH: 43.1-10.7 vs. Nx: 6.1-3.4 m, p=0.012) and at later time points. Subgroup analysis demonstrated that IH enhances walking speed, endurance, and up and go time in both ASIA C and D subjects, with no statistical differences between ASIA subgroups at all time points (p > 0.05).

In the study of Raithatha et al, 2016 the purpose was to investigate the effects on neuroplasticity of pairing transcranial direct stimulation (t-DCS) with LT-RGO in people with chronic, incomplete SCI[16]. The primary outcome measure was manual muscle testing (MMT). Secondary outcome measures included 10MWT, 6MinWT, Timed Up and Go Test (TUG), Berg Balance Scale (BBS), and Spinal Cord Independence Measure III. In the study, 15 people with spinal cord injuries participated, who were randomly separated in 2 groups, LT-RGO+ tDCS and LT-RGO+ sham-tDCS. The active group improved significantly compared to the sham group on the primary outcome measure MMT. The sham tDCS group improved significantly compared to the active tDCS group on 6MinWT and TUG. Between-groups comparison of changes from baseline to 1-month follow-up revealed significantly greater improvements in MMT (right LE) for the active tDCS group. An ANCOVA model used to measure baseline differences showed treatment effect at a 95% confidence interval for MMT (right LE) at both post-intervention and at 1-month follow-up as well as a significant advantage for the sham tDCS group in SCIM-III in 1-month follow-up. This study supports the feasibility of using tDCS in conjunction with a novel LT-RGO protocol that targets corticospinal plasticity to optimize gait recovery for people with SCI.

Conclusion

There is a need to develop physical therapy interventions that can effectively engage spared neural connections to further improve functional recovery in humans with SCI. According to the results of the 6 randomized control trials included in our study, interventions such as massed practice with somatosensory stimulation, Exercise with corticospinal neural stimulation, endurance training, intermittent hypoxia (IH) combined with Body weight supported treadmill training and Paired transcranial direct current stimu-

lation (tDCS) with Locomotor training with a robot-assisted gait orthosis (LT-RGO) can enhance neuroplasticity and induce functional recovery in people with SCI. Therefore, further research needs to be done.

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