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Special Review

Updates in Neurorehabilitation

Update on Stroke Rehabilitation for Non-Motor Impairment

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HIGHLIGHT

- Various stroke rehabilitations are investigated to treat non-motor impairments.
- Non-invasive brain stimulation and virtual reality are the most common treatments.

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ABSTRACT

Various interventions exist to treat non-motor impairments caused by stroke. Adjuvant treatments such as non-invasive brain stimulation, virtual reality, computer-assisted training, neurostimulation, and biofeedback are being investigated and applied in the areas of cognitive dysfunction, language problems, visual disorders, dysphagia, mood disorders, and post-stroke pain. Most of these treatments have shown efficacy and symptom improvement, but further investigation is required to fully clarify their effects.

Keywords: Stroke Rehabilitation; Cognitive Dysfunction; Language Disorder; Visual Disorder; Dysphagia

INTRODUCTION

Stroke is the primary reason for adult disability. The global prevalence of stroke-related disability has increased over recent decades because of population growth and aging [1]. Stroke-related disability can be categorized into motor and non-motor impairments. Motor impairments, such as hemiplegia, are the most noticeable sequelae. However, non-motor impairments, such as cognitive deficits, language impairment, visual disorders, dysphagia, mood disorders, and pain can cause far greater decreases in quality of life [2]. Nonetheless, treatment of non-motor impairments has drawn less attention than that of motor impairments. However, various interventions exist to treat non-motor impairments caused by stroke. In this review, we discuss recent updates in stroke rehabilitation for non-motor impairments.

COGNITION

Cognitive dysfunction is common after stroke. This dysfunction is a direct result of the stroke lesion, hypoperfusion around the lesion, and disrupted connections between white matter and cortical regions [3]. A recent review covered several neurotechnologies used to treat stroke patients with cognitive dysfunction [4]. Computerized cognitive training was the most common intervention discussed, but treated patients still had difficulty adapting to daily life activities. Another intervention mentioned in the review is virtual reality (VR). Immersive VR was found to be more effective and better at encouraging motivation than non-immersive VR. VR is advantageous in that it offers a chance to practice real-life activities in a safe and secure environment. Non-invasive brain stimulation (NIBS) showed promising outcomes, but not enough to make conclusive statements. Neurofeedback with brain-computer interfaces also showed promise, but practical and clinical translation is necessary.

Computer-assisted cognitive rehabilitation is a form of cognitive training for memory, attention, working memory, language, and processing speed. It involves variable resources such as specific software systems or hardware tools. A meta-analysis found that computer-assisted cognitive rehabilitation was effective after stroke [5]. The analysis included 32 studies and a total of 1,837 patients. Computer-assisted cognitive rehabilitation was significantly superior to conventional therapy in improving patients' global cognition. The patients were evaluated via the Mini-Mental State Examination (mean difference [MD], 2.51; 95% confidence interval [CI], 1.94 to 3.08; $p < 0.00001$), the Montreal Cognitive Assessment (MD, 2.67; 95% CI, 2.21 to 3.13; $p < 0.00001$), and the Loewenstein Occupational Therapy Cognitive Assessment (MD, 8.63; 95% CI, 4.99 to 12.28; $p < 0.00001$). Based on the study, sufficient evidence exists to support the use of computer-assisted cognitive rehabilitation for the treatment of stroke patients.

In non-invasive brain stimulation, magnetic or electrical current is utilized to non-invasively alter the excitability of the underlying brain cortex and potentially trigger long-term neuroplastic alterations. In a meta-analysis of the effect of NIBS on cognition in stroke patients [6], researchers reviewed six studies including 221 patients treated with repetitive transcranial magnetic stimulation (rTMS) and four studies including 196 patients treated with transcranial direct current stimulation (tDCS). The most frequent stimulation sites were the dorsolateral prefrontal cortex (DLPFC) in the rTMS studies and the frontal lobe in the tDCS studies. In the meta-analysis, rTMS was associated with significant improvements in attention (standardized mean difference [SMD], 1.40; 95% CI, 0.36 to 2.44; $p = 0.008$), memory (SMD, 0.76; 95% CI, 0.17 to 1.35; $p = 0.01$), working memory (SMD, 1.35; 95% CI, 0.95 to 1.76; $p < 0.00001$), and cognition (SMD, 1.31; 95% CI, 0.87 to 1.75; $p < 0.00001$), but high heterogeneity was reported among trials for attention and memory. In contrast, for tDCS, no significant heterogeneity was reported, but the technique was not found to be effective. The effect of rTMS was likely due to the use of the DLPFC as the stimulation site. In several studies, the DLPFC has been found to be associated with attention, working memory, and the central executive network [7-9]. Therefore, to treat cognitive impairment after stroke, the DLPFC may be the most appropriate stimulation site. In most of the studies involving high-frequency rTMS, stimulation was applied over the left DLPFC, with protocols ranging from 5 to 10 Hz, 80% to 100% motor threshold, 600 to 2,000 pulses per session, and 10 to 20 sessions. All of the studies of high-frequency rTMS showed improvement in cognition. However, the studies involving low-frequency rTMS demonstrated no significant impact on cognition. These trials delivered 1 Hz, 100% motor threshold, and 600 to 900 pulses per session for 10 to 20 sessions. Bilateral tDCS was applied in two studies, anodal tDCS in one, and dual tDCS in one. The stimulation parameters were 2 mA per 25 to 35 cm^2 for 30 minutes per session, from 12 to 18.5 sessions. No unified consensus emerged regarding the optimal NIBS parameters for cognition treatment after stroke, but excitatory stimulation of the DLPFC or frontal lobe generally seemed to be most effective. However, evidence is still limited.

Virtual reality provides users with interactive simulation in a realistic environment. VR technology has been increasingly applied in stroke rehabilitation. In a recent meta-analysis on the use of VR after stroke, VR interventions appeared effective in improving upper- and lower-limb motor function, balance, gait, and daily function, but they had no significant effects on cognition [10]. Across seven studies, mini-mental state examination revealed no significant effect of VR compared to controls (MD, 0.81; 95% CI, −0.41 to 2.03; p = 0.19). In two studies, no significant differences were found between the VR and control groups on the auditory continuous performance test (MD, 0.03; 95% CI, −0.12 to 0.17; p = 0.74) or the visual continuous performance test (MD, −0.03; 95% CI, −0.09 to 0.02; p = 0.20). The authors proposed that this lack of significant impact on cognition may exist because current VR interventions were developed for purposes other than cognitive training. Thus, the use of an inadequate VR program not tailored for the treatment of post-stroke cognitive impairment may primarily explain the ineffectiveness.

LANGUAGE

Language disorders, such as dysarthria or aphasia, are very common after stroke. Dysarthria causes weakness and impaired or uncoordinated movements of the muscles, lips, tongue, jaw, throat, vocal folds, and diaphragm when producing speech. Dysarthria is characterized by slurred, slow, breathless, and/or imprecise speech. Aphasia is the inability to formulate and/or comprehend language because of damage to specific brain regions [11].

In a recent meta-analysis of dysarthria after stroke, the effectiveness of speech rehabilitation was analyzed [12]. Thirty-seven publications were reviewed, and speech therapy was shown to effectively improve acoustic parameters. The alternating motion rate (AMR)-Pə (SMD, −0.614; 95% CI, −1.056 to −0.171; p = 0.007), AMR-Tə (SMD, −0.512; 95% CI, −0.095 to −0.0734; p = 0.023), and AMR-Kə (SMD, −0.497; 95% CI, −0.936 to −0.0584; p = 0.027); the sequential motion rate-PəTəKə (SMD, −0.663; 95% CI, −1.109 to −0.217; p = 0.004), and the maximum phonation time (SMD, −0.736; 95% CI, −1.258 to −0.215; p = 0.006) significantly improved after speech rehabilitation. In the review, various examinations were used to measure dysarthria severity, including physical examination, intelligibility scales, neuropsychological and cognitive tests, multi-dimensional voice program and Praat software, and neuroimaging. Furthermore, various speech therapies were used, such as traditional rehabilitation speech therapy, Lee Silverman voice treatment, accent-based music-speech protocol, tDCS, rTMS, and others. However, the current literature reported no guidelines for the clinical assessment or treatment of subjects with post-stroke dysarthria.

Regarding aphasia, a review covered adjunctive approaches to aphasia rehabilitation [13]. The review provided an overview of the pharmacological approach, VR, and tDCS in the treatment of aphasia after stroke. For the pharmacological approach, 31 articles were reviewed. Piracetam, donepezil, galantamine, memantine, levodopa, bromocriptine, and amphetamines were used in combination with conventional language treatments. Among those drugs, only bromocriptine was studied primarily as a replacement for speech therapy. However, evidence of positive effects was minimal, and possible adverse effects were reported. In addition, the therapeutic mechanisms of these drugs are still unclear. Regarding VR, 8 articles were reviewed. While VR applications for aphasia rehabilitation are in their infancy, they are still promising. An advantage of VR is the possibility of self-administration, which may enhance self-esteem, self-efficacy, independence, and responsibility. A VR environment can also emphasize sensorimotor properties more easily than a usual language therapy setting, allowing VR to provide semi-immersive, multimodal dimensional interactions. The review also proposed that the patients in question can communicate beyond their linguistic abilities; along those lines, VR could promote functional communication in an ecological context. For tDCS, 37 articles were reviewed. To correct unbalanced hemispheric interaction between the remaining language areas and the other hemisphere, 2 broad electrode placement approaches were applied. Anodal stimulation facilitates electrical activity in lesioned or perilesional areas, while cathodal stimulation inhibits the intact hemisphere by diminishing unbalanced transcallosal inhibition. In most of the studies, anodal stimulation was applied over the left Broca, left Wernicke, or right homologous areas combined with speech therapy. The majority of the studies revealed improvement in naming, and some showed effectiveness in fluency, repetition, and reading. The advantages of tDCS were cost-effectiveness, low rates of adverse effects, and ease of use. In the review, most of the studies involved the application of anodal tDCS, while approximately half of that number involved cathodal tDCS. Four studies involving dual stimulation were recently published. These studies had substantial heterogeneity in the number of sessions, ranging from 1 to 15. The intensity was less variable, with studies tentatively aligning on 1 to 2 mA. Regarding stimulation site, the review did not conclusively point to a specific site, but the left perilesional area appears to be suitable. Furthermore, right homologues are also available.

In cases of aphasia after stroke, rTMS is another option among NIBS approaches. A recent meta-analysis was focused on rTMS in the treatment of post-stroke aphasia [14]. The analysis included 28 studies with a total of 1,287 patients. rTMS treatment was associated with significantly lower aphasia severity than either sham rTMS (SMD, 0.44; 95% CI, 0.04 to 0.83; $p = 0.03$) or conventional rehabilitation (SMD, 3.77; 95% CI, 2.00 to 5.54; $p < 0.0001$). In naming, the rTMS group showed significantly more improvement than the sham rTMS (SMD, 0.53; 95% CI, 0.30 to 0.76; $p < 0.00001$) or conventional rehabilitation group (SMD, 0.56; 95% CI, 0.18 to 0.93; $p = 0.004$). Regarding repetition, rTMS treatment had significantly better outcomes than sham rTMS (SMD, 0.56; 95% CI, 0.30 to 0.81; $p < 0.0001$) and conventional rehabilitation (SMD, 0.81; 95% CI, 0.34 to 1.28; $p = 0.0008$). For comprehension, rTMS was significantly superior to conventional rehabilitation (SMD, 0.85; 95% CI, 0.13 to 1.56; $p = 0.02$). Regarding spontaneous speech, rTMS was significantly better than both sham rTMS (SMD, 0.70; 95% CI, 0.09 to 1.30; $p = 0.02$) and conventional rehabilitation (SMD, 0.72; 95% CI, 0.29 to 1.14; $p = 0.001$). rTMS was also associated with greater improvements in aphasia quotient than either sham rTMS (SMD, 1.11; 95% CI, 0.43 to 1.79; $p = 0.001$) or conventional rehabilitation (SMD, 0.85; 95% CI, 0.53 to 1.16; $p < 0.00001$). In the subgroup analysis, low-frequency rTMS was found to be more effective than sham rTMS with regard to aphasia severity, spontaneous speech, repetition, naming, and aphasia quotient. In language recovery, low-frequency and bilateral rTMS were more effective than conventional rehabilitation. However, high-frequency rTMS did not differ significantly from either sham rTMS or conventional rehabilitation. In comprehension, naming, and aphasia quotient, as the number of sessions increased, the effect of rTMS also increased. Furthermore, it was particularly effective at 20 sessions. The effects of high-frequency and bilateral rTMS must be clarified by additional research; however, the study suggested that the small number of studies on high-frequency rTMS was attributable to the greater risk of seizure compared to low-frequency rTMS.

VR may have potential benefits in patients with post-stroke aphasia by offering abundant virtual environments, prompt feedback, and participation in high-intensity task-oriented rehabilitation [15]. VR may also safeguard effective rehabilitation by alleviating the shortage of therapists. In a recent meta-analysis, the effects of VR were evaluated in the treatment of post-stroke aphasia [16]. Five studies including a total of 121 participants were reviewed. VR was associated with a decrease in the severity of language impairment of borderline significance (SMD, 0.70; 95% CI, 0.01 to 1.39; $p = 0.05$). However, no significant differences were found in functional communication, repetition, and word finding. As VR for aphasia rehabilitation was still at an early stage at the time of the review, VR did not improve functional communication, which was considered the primary outcome. However, a borderline effect was shown in the severity of language impairment. Borderline significance often results from an insufficient number of participants. Therefore, the study authors insisted that well-designed future studies with larger samples are necessary.

VISUAL DISORDERS

Cortical blindness, such as homonymous visual field defects, can result from multiple neurologic insults, with stroke as the most common etiology [17]. In a recent review of advances in rehabilitation for visual field defects after stroke, the compensation, substitution, and restoration approaches were discussed [18]. Compensation therapy involves explicit coaching to make more eye and head movements to check the blind spot. Compensation therapy has increasingly been administered through internet-based programs. Various programs encouraged eye movements, and the patients improved in error rate, search time, self-reported disability score, and activity of daily living [19]. However, these studies lacked control groups. Augmented reality and VR are also emerging. Substitution therapy is designed to redirect visual information into the intact hemifield, such as with a Fresnel prism lens. However, due to adverse effects like diplopia and headache, only one-third of those who participated in a prism rehabilitation program continued to use their lenses in the long term [20]. Additional substitution devices such as specialized goggles are under investigation. Restoration therapy is a strategy to restore conscious visual perception and diminish the size of the defective visual field. Multiple groups have applied computerized training programs and have reported improvements. The programs consist of a stimulus that is presented inside the blind field and detection, discrimination, or identification of each stimulus. NIBS is being investigated as an adjuvant rehabilitation method in the treatment of cortical blindness. Visual restoration training combined with tDCS was associated with a decrease in field defects, as well as improvements in motion perception and activity of daily living [21,22]. In another study, transcranial random noise stimulation was applied; compared to sham stimulation, it was associated with more rapid improvements in complex motion discrimination in patients' blind fields [23]. Finally, when transorbital alternating current stimulation was combined with visual restoration training, enhanced contrast sensitivity in the central visual field was observed [24].

Spatial neglect is another form of visual impairment after stroke. A recent meta-analysis focused on prism adaptation as a treatment for spatial neglect [25]. Eight studies involving a total of 244 patients were reviewed. Overall, prism adaptation improved the neglect symptoms of post-stroke patients in the short term as indicated by the star cancellation test (MD, 3.04; 95% CI, 0.19 to 5.88; $p = 0.04$) and the behavioral inattention test (MD, 8.99; 95% CI, 0.93 to 17.06; $p = 0.03$), but it had no significant long-term effects per the behavioral inattention test (MD, 8.93; 95% CI, −1.98 to 19.84; p = 0.11). The authors attributed this lack of long-term impact to the prism, mainly improving the spatial bias of unilateral neglect, while perception of the visual stimulus on the neglect side was unchanged. Thus, the patients were still incapable of recognizing the stimulus on the neglect side. Another potential reason was the not inclusion of a placebo condition in the studies. In a randomized controlled trial, VR was applied among stroke patients with spatial neglect [26]. The study included 24 stroke patients with unilateral spatial neglect who were randomly allocated into a VR and a control group (12 patients each). The VR group was administered VR-based digital practice in 30-minute sessions, with 3 sessions per week for 4 weeks. The VR group displayed better performance than the control group, as indicated by the line bisection test, the Motor-Free Visual Perception Test Vertical Version, and head rotation and rotation velocity data obtained via head tracking sensor. The authors suggested that VR application may have stimulated interest and participation by providing immediate 3-dimensional feedback, causing the patient to concentrate more for a prolonged period. The increased attention and arousal may have helped mitigate spatial neglect.

DYSPHAGIA

Dysphasia is common after stroke, and lesions in the cortex, subcortex, and brainstem can result in swallowing difficulty. A review covered the management of post-stroke dysphagia [27]. Traditional dysphagia treatment after stroke has focused on the rehabilitation strategies of compensation and behavioral adaptation. As the understanding of dysphagia recovery has evolved, novel treatment methods have been developed. Two major treatments are neurostimulation and biofeedback.

Neurostimulation is categorized into peripheral stimulation, central stimulation, and paired associative stimulation. In peripheral stimulation, such as pharyngeal electrical stimulation (PES), low-amplitude electrical impulses are used to passively stimulate the pharynx. PES appears to increase the activity of the regions involved in swallowing, potentially facilitating motor cortex reorganization [28]. Neuromuscular electrical stimulation is another example of peripheral stimulation. Electrical stimulation is applied via a transcutaneous electrode, causing the suprahyoid or infrahyoid muscles to contract. Suprahyoid stimulation leads to elevation of the hyoid bone and larynx by activating the mylohyoid, geniohyoid, and anterior belly of the digastric muscles. In contrast, infrahyoid stimulation leads to depression of the hyoid bone and larynx by activating the omohyoid, sternohyoid, and sternothyroid muscles. Suprahyoid stimulation appears to strengthen the weak muscles and elevate the hyolaryngeal complex to protect the airway for swallowing, while infrahyoid stimulation depresses the hyolaryngeal complex as a mechanism to swallow against resistance [29]. Next, central stimulation methods include rTMS and tDCS. In rTMS, both high- and low-frequency modalities were applied to manage post-stroke dysphagia. Regarding tDCS, researchers have evaluated unilateral anodal tDCS, bilateral tDCS, and dual stimulation. Finally, paired associative stimulation involves the simultaneous application of peripheral and central stimulation to excite the pharyngeal motor cortex. In a recent meta-analysis, neurostimulation was reported to be effective [30]. Twenty-seven studies with a total of 914 stroke patients were included. The meta-analysis showed that patients treated with non-invasive neurostimulation (rTMS, tDCS, surface neuromuscular electrical stimulation, or PES) had significantly better outcomes (SMD, 0.91; 95% CI, 0.54 to 1.27; p < 0.00001) than control participants. In a subgroup analysis by stimulation type, rTMS was more effective than tDCS (SMD, 1.27; 95% CI, 0.59 to 1.95; p = 0.0003), potentially due to the stimulation depth. Both tDCS and rTMS involve the use of electric current to stimulate specific nerve sites, but the stimulation depth is generally around 1 cm in tDCS, while rTMS reaches up to 6 cm [31]. Regarding stroke chronicity, neurostimulation applied at the acute phase was particularly effective (SMD, 1.35; 95% CI, 0.27 to 2.42; p = 0.01). Treatment was also more effective for brainstem lesions (SMD, 1.53; 95% CI, 0.49 to 2.57; p = 0.004) than unilateral hemisphere lesions. Regarding stroke type, the cerebral infarction group showed better improvement (SMD, 1.75; 95% CI, 0.78 to 2.72; p = 0.0004) than the group with infarction and hemorrhage. For NIBS in the treatment of post-stroke dysphagia, the appropriate stimulation site and frequency or polarity are still under debate. Additionally, depending on the site and frequency, various recovery mechanisms may be considered, including interhemispheric inhibition, non-affected hemisphere compensation, and bimodal balance. Among these, the interhemispheric inhibition model appears to be fundamental. Therefore, high-frequency rTMS and anodal tDCS should be utilized on the lesion side and low-frequency rTMS and cathodal tDCS on the non-lesion side. However, other recovery mechanisms have also been proposed, and studies to ascertain the most appropriate approaches are still needed.

Biofeedback alters the swallowing process and improves swallowing performance by providing visual or auditory signals to patients. In post-stroke dysphagia, surface electromyography is the most common biofeedback technique. Two surface electrodes are attached to submental muscles to evaluate the force and timing of muscle contraction. The measurements are presented graphically on a screen. In a recent meta-analysis, surface electromyography biofeedback with swallowing maneuvers was shown to improve the degree of the displaced hyoid bone in case of post-stroke dysphagia compared to controls [32].

MOOD

Stroke can cause several mood disorders, most commonly post-stroke depression (PSD). Approximately 30% of stroke patients may have PSD [33]. In a recent review, no unified mechanism emerged to explain PSD. However, several pathophysiologies were discussed, including dysregulation of the hypothalamic-pituitary-adrenal axis, increased levels of inflammatory factors, decreased levels of monoamines, glutamate-mediated excitotoxicity, and an abnormal neurotrophic response [34]. PSD has 2 traditional treatment methods: pharmacotherapy and psychological therapy. In a recent review, pharmacotherapy was described as the primary method to treat PSD. Selective serotonin reuptake inhibitors are the first-choice drugs due to their relatively mild adverse effects; tricyclic drugs are considered second-line therapy due to their severe side effects and contraindications [35]. In psychological therapy, cognitive behavioral therapy has been found to be effective for PSD. In addition, rTMS is a novel technique for PSD treatment. Low-frequency rTMS at 0.5 Hz over the DLFPC is an accepted treatment protocol for PSD. In a recent study, accelerated rTMS was found to be a safe and effective treatment for PSD [36]. The typical conventional rTMS protocol consisted of 20 sessions, with 5 sessions per week for 4 weeks. However, an accelerated protocol condensed these 20 sessions into 4 consecutive days. After accelerated rTMS, scores on the Hamilton depression rating scale (reported as the mean±standard deviation) significantly decreased from 15.5 ± 2.81 to 4.17 ± 0.98, and the effect persisted at the 3-month follow-up. Furthermore, emerging drugs and therapies for PSD exist, such as escitalopram, VR, transcranial alternating current stimulation, and iPad applications, among others [37].

PAIN

Both neuropathic and nociceptive mechanisms can cause post-stroke pain. The most common type of post-stroke pain is musculoskeletal, affecting up to 72% of stroke patients [38]. Post-stroke pain syndromes are reported in up to 30% of stroke survivors [39]. Post-stroke pain syndrome includes central post-stroke pain (CPSP), pain secondary to spasticity, shoulder pain, complex regional pain syndrome, and headache. A recent review reported the use of opioids in the treatment of post-stroke pain [40]. Across 8 articles, researchers assessed the effects of morphine, levorphanol, and the opioid antagonist naloxone in cases of CPSP, with slight analgesic effects. However, meta-analysis did not show a significant effect compared to the control group (relative risk, 1.05; 95% CI, 0.57 to 1.92; $p = 0.88$). The poor response of CPSP to opioids is likely due to the reduced binding capacity of opioids in the pain circuitry in patients with CPSP. In addition, stroke patients may have communication issues, causing difficulties describing their pain. Another study reviewed the effectiveness of injection therapies for hemiplegic shoulder pain after stroke [41]. A total of 17 studies involving 595 participants were included. Injection therapies included intrabursal botulinum toxin (BoNT), intramuscular BoNT, suprascapular nerve block (SSNB), intra-articular steroid, and hyaluronic acid injection. According to surface under the cumulative ranking area analysis at week 4, SSNB was associated with the greatest decrease in the visual analogue scale for pain. Between weeks 4 and 24, however, intramuscular BoNT was the most effective in visual analogue scale pain reduction. The clinical effect of SSNB is provided by local anesthetics. However, as spasticity is the leading cause of persistent hemiplegic shoulder pain, intramuscular BoNT was the superior option between weeks 4 and 24.

CONCLUSION

In the current review, the most frequently studied stroke rehabilitation method for non-motor impairment was NIBS. NIBS was demonstrated to be effective in the treatment of cognition, language, visual disorders, dysphagia, and depression. VR was the second most common and was effective in the treatment of language and visual disorders. For some impairments, such as mood disorders and pain, medical therapy is mainstream. However, all of the adjuvant therapies seem to be effective only when used with conventional rehabilitation. In addition, the level of evidence and quality of most studies are insufficient. Therefore, further well-established investigations may be needed to fully ascertain the effects of each method of stroke rehabilitation for non-motor impairment.

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