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Review Article

Constraint-induced movement therapy as a paradigm of translational research in neurorehabilitation: reviews and prospects

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Abstract: There is an increasing awareness about the importance of translation from basic scientific findings into practical application for efficiently improving human health, especially in the pharmaceutical industry. In the field of neurorehabilitation, however, the bench-to-bedside process continues to be developing, and thus most of the therapeutic interventions have encountered barriers during exploration of evidence-based effectiveness. Despite this immaturity, constraint-induced movement therapy (CIT), a well-evidenced treatment evolved from research in nonhuman primates, is suggested to be an ideal paradigm of translational research in the field of neurorehabilitation. This article reviews the evolvement of CIT with regards to its behavioral efficacy and neuroimaging evidence through the translation roadmap developed by the National Institutes of Health. We also discuss prospects for the application of combined interventions, such as stem cell therapy or pharmaceutical prescription, with appropriate screening of patients beforehand, as well as an efficient delivery mode after the treatment. To achieve such goals and consolidate evidenced-based neurorehabilitation, we provide a framework for applications into the translational research of other therapeutic interventions aside from CIT.

Keywords: Neurorehabilitation, constraint-induced movement therapy, neuroimaging, translational medicine, neuroplasticity

Introduction

Neurorehabilitation is a complex medical process based on knowledge of neurology and neuroscience. It aims to boost recovery from injury to the nervous system and to minimize and/or compensate for any functional alterations that follow. Neurorehabilitation is often categorized as rehabilitation, but the definitional boundary between them remains unclear. Compared with other areas of science involved in rehabilitation, such as biomechanics or psychosocial theory [1-2], neurorehabilitation emphasizes improvement of the nervous system during the medical process, and it has been reckoned that the recovery of sensorimotor and psychosocial function comes from convalescence of the nervous system.

One critical point of advancing neurorehabilitation is to translate the findings of neurology and neuroscience research into medical therapies for patients with neurologic diseases [3]. However, many gaps exist between basic science and clinical application that hinder an effective translation from knowledge to treatment. To solve these difficulties, translational research can be an itinerary to guide scientists and clinical practitioners to facilitate the process of translation [4]. Translational research means "bench-to-bedside", that is, how to harness knowledge of basic science to develop new drugs, devices, and treatment options for patients [5]. Translational research can also be

used by public health investigators and health service researchers and may help improve the outcome of health care. Here, translational research plays a role in applying scientific results into everyday clinical practice and health decision making [6]. Westfall and colleagues offered an explicit process of translation research illustrating the cascade from bench to bedside to clinical practice and the specific categories of research in each translational phase for investigators to follow [7]. The process of translational research is bidirectional; that is, the advance is not only from bench to bedside to practice but also vice versa. New discoveries of basic science have been regarded as the theoretic foundation of clinical research and application; however, findings about behavior change or effectiveness at the bedside may also bring inspiration to basic research [8].

There are many common grounds between development of neurorehabilitative therapies and discovery of new drugs. They both eagerly require a great deal of basic research as the knowledge base to develop new therapies or drugs and need well-designed and large-scale research to establish therapeutic guidelines and prove efficacy. Discoveries of new drugs are based on pharmacology and molecular biology to progress the hypothesis testing by experiments on homogenous animals in the laboratory. However, the development of neurorehabilitative therapies is more complicated because neurobehavioral science, which provides the background knowledge of neurorehabilitation, does not solely rely on neurobiology but also on high-level cognitive functions such as learning, languages, and even cultures. It is an arduous task to simulate the mechanism of impairments with experimental animals, and thus, the barrier has impeded the evolution of neurorehabilitation. Accumulating knowledge about neural recovery by noninvasive and real-time brain imaging has recently promoted the development of new neurorehabilitative therapies and has been expected to foster personal medical care in the future [9].

In the past few years, a number of multicenter randomized clinical trials, including the Extremity Constraint-Induced Therapy Evaluation (EXCITE), Spinal Cord Injury Locomotor Trial (SCILT), and Robot-Assisted Therapy for Long-Term Upper-Limb Impairment after Stroke [10-12], have been developed as good paradigms of translational research in the field of neurorehabilitation. Constraint-induced movement therapy (CIT) was derived from learned-nonuse phenomenon observed in nonhuman primates by Taub and colleagues in 1958 [13]. Based on the theory that comes from research on monkeys, CIT has evolved to be applied on patients for restoring motor function due to various neurologic diseases [14-15]. The effectiveness of CIT was further evaluated in real medical conditions through several multicenter randomized clinical trials [12]. Hence, CIT is deemed as an excellent paradigm of translational research with regards to neurorehabilitation therapies.

The purpose of our study was to review the translational process of CIT, a prominent example of neurorehabilitation based on the roadmap illustrated by Waterfall and colleagues. We started by clarifying how primate research has been translated into clinical research of CIT and then reviewed evidence about the effects reported in multicenter randomized clinical trials. Furthermore, we elaborated on the evidence about neuroplastic change after CIT and the advances in the translational process with respect to outcome prediction and patient selection that may facilitate the development of personalized rehabilitation therapies.

CIT—the comparatively mature translational model in neurorehabilitation pertaining to effectiveness

As mentioned, advancement in the field of rehabilitation has been painstakingly slow compared with pharmaceutical or other biologic fields. However, thanks to the abundant academic harvest in CIT, it has become an exceptional model that can be fit into the National Institutes of Health roadmap for medical research brought up by Westfall and colleagues [7]. The roadmap includes 3 major research laboratories: bench, bedside, and practice. The research pertaining to the "practice'' phase has not yet been developed compared with the other 2 laboratories. The bridges connecting these laboratories are "translation to humans,'' "translation to patients,'' and "translation to practice.'' In **Table 1**, we summarize the development of CIT in the translational process and the efficacy of CIT in human patients.

CIT has systematically evolved since the phenomenon called "learned nonuse" was ob-

Table 1. Development of constraint-induced movement therapy - the process of translation from bench to bedside

Phase of Translational Research	Research Type	Examples
Basic Science Research	Laboratory experiment	• The observation and explanation of learned nonuse in monkeys with deafferented upper extremity and the positive efficacy after applying forced use paradigm on the hemiplegic monkey [17, 18] • The effectiveness of CIT on ICH rats that CIT when combining with environment enrichment and task-specific training [37]
Translation to human phase	One or two group pretest-posttest design	• Examination of efficacy by applying forced use paradigm on one hemiplegic patient or a small group of stroke and TBI patients [19, 20] • Examination of efficacy by controlling characteristic of the samples such as time after onset and severity of hemiparesis [21,22] • The efficacy of CIT on different parts on upper extremity was examined and the hand was the most benefited one [24]
Human clinical research	Randomized controlled study ❶Placebo-controlled trial ❷Conventional intervention controlled ❸New-developed intervention controlled	❶CIT vs. a program of physical fitness, cognitive, and relaxation exercises [23] ❷CIT vs. traditional occupational therapy such as ADL, ROM, strength training [25] ❸CIT vs. Bilateral arm training [27]
Translation to patients phase	❶Systematic review ❷Guideline development	❶ Systematic reviews of randomized controlled trials on the adult stroke patients, pediatric and cognitive application [29,30,35,36] ❷Intervention protocol for CIT [31]
Practice-based research	One or two-group pretest-posttest design	• Pain, fatigue, and intensity of therapy were evaluated and compared between subacute and chronic group [32] • Different training schedules of CIT were examined by varying the duration or intensity of the treatment [33]
Translation to practice phase	Perspectives for clinical application	• Integrated approaches combining CIT with robotics, virtual environments, mental imagery, pharmaceutical manipulations and cortical stimulation [34] • Screening of appropriate clients, delivery mode, reimbursement concerns and follow-up out of the clinic [34]

CIT: constraint-induced movement therapy, ICH: intracerebral hemorrhage, TBI: traumatic brain injury, ADL: activities of daily living, ROM: range of motion.

served in Taub's research on monkeys, although such conditioned failure of functional limb use was first described as "limb amnesia" by Meige early in 1904 [16]. Taub and colleagues later discovered that the phenomenon of learned nonuse could be reverted when monkeys were restrained to use their deafferented limbs while applying shaping strategies. Furthermore, the recovery in function could be long-lasting if the restraint was maintained for 1 to 2

weeks [17-18].

CIT has gained increasing popularity in the past 2 decades because it represents one major advance in evidenced-based neurorehabilitation therapy evolved from basic research. Functional recoveries in humans after CIT were first demonstrated by Ostendorf and Wolf in a single-case design study, where they implemented forced-use therapy of the hemiplegic upper extremity on a stroke patient [19]. Expanding previous work, Wolf and colleagues found significant changes in several motor tasks in 21 chronic stroke or traumatic brain injury (TBI) patients at the 1-year follow-up and demonstrated that the learned nonuse phenomenon can be reverted through the forced use paradigm [20].

As a preliminary stage of translational research process, pretest-posttest design was conducted in several clinical studies and applied to different patients (eg, different characteristics of time after onset and severity of hemiparesis) or by implementing modified CIT protocols by changing the intensity and duration of treatment regimen. For instance, different from most previous studies about CIT effectiveness on chronic stroke patients, Dromerick and colleagues demonstrated that CIT could also be effectively applied on acute stroke patients (14 days after onset). However, later studies performed by Boake and colleagues showed conflicting results of applying CIT on patients with acute stroke [21]. Aside from time after onset, improved motor function was noted in the involved upper extremity of a patient with severe hemiparesis after CIT, although the client reported no progress in functional use in the study of Bonifer and Anderson [22].

CIT showed substantial potential in several uncontrolled studies to assist stroke patients with improving their upper extremity function. However, large randomized clinical trials were desperately needed to clarify the benefits of this intervention and maximize the effectiveness. Taub and colleagues conducted a placebo-controlled trial of CIT for the upper extremity after stroke. Patients with chronic stroke showed large improvements in the functional use of their more affected arm in their daily lives after CIT, whereas placebo subjects who received a program of physical fitness, cognitive, and relaxation exercises showed no significant changes [23]. As many past studies have demonstrated, CIT is most beneficial to the intervention on the upper extremity, and Koyama and colleagues further examined which part of the upper extremity can get the most benefit from the treatment. They found that CIT is most beneficial for improving hand function in their pretest-posttest analysis [24].

Randomized controlled studies comparing effectiveness among CIT and different interventions (ie, comparative effectiveness research) may provide more solid evidence for the efficacy of CIT. CIT was preliminarily compared with occupational therapy (such as activities of daily living, range of motion, and strength training) in the study of Dromerick and colleagues, and the results showed significant improvement in pinch strength after 2 weeks of CIT but no significant difference in outcome measures after traditional intervention [25]. Furthermore, a single-blind randomized clinical trial conducted by Vander Lee and colleagues compared CIT with treatment that applied bimanual activities in a sample of 66 stroke patients [26]. Significant differences were found in the outcome measures, and the beneficial effect was especially significant for patients with sensory disorder and hemineglect [25]. In addition, according to the recent findings of Lin and colleagues, bilateral arm training may uniquely improve motor impairment of the proximal upper extremity, whereas distributed CIT may produce greater functional gains for the affected upper limb in individuals with mild to moderate chronic hemiparesis [27].

Major progress in the translational evolution of CIT has been reported in the large controlled trial of EXCITE that comprehensively studied the effects of CIT in objective functional performance and self-reported outcomes in as many as 222 patients with stroke. In the EXCITE trial, Wolf and colleagues found that CIT produced statistically significant improvement in arm motor function, which persisted for at least 1 year among patients who had a stroke within the previous 3 to 9 months in comparison with those who received customary care [12]. In recent work related to modified CIT in subacute stroke patients, Lin and colleagues have found that increased motor function, basic and extended functional abilities, as well as quality of life were demonstrated after modified CIT intervention (intensive training and wearing restraint

out of clinic) compared with a control group that received conventional rehabilitation and had been wearing a restraint out of the clinic [28].

Because the results from studies supporting the application of CIT in patients have continue to increase during the past decade, systematic review and guidelines for intervention are desperately needed to help clinical practitioners provide more stable and standardized intervention as well as apply it efficiently into real therapeutic contexts and even daily life out of the clinic [29-30]. Morris and colleagues presented a detailed description of the CIT protocol by dissecting CIT into many components and subcomponents, such as repetitive, task-oriented training, adherence-enhancing behavioral strategies, and constraining use of the more affected upper extremity. They also gave examples instructing how to transfer gains made in the clinical setting to the client's real-world environment [31]. It is a representative example belonging to the "translation to patients phase," providing a concrete framework for those who are concerned.

In addition, with increasing awareness of improving quality of life and trends emphasizing client-centered medical care, practice-based research and work on translation to practice phase have gradually developed in recent years. For instance,

Underwood and colleagues evaluated pain, fatigue, and intensity of CIT and compared the result between subacute and chronic stroke patients. They concluded that the intensive practice associated with CIT may be administered without exacerbation of pain or fatigue, even early during the recovery process [32]. Different training schedules were also examined by a study performed by Sterr and colleagues. They found that the modified 3-hour CIT training schedule significantly improved motor function in chronic hemiparesis but was less effective than the traditional 6-hour training schedule [33].

In addition, Wolf and colleagues have brought up and discussed several aspects of consideration about CIT application, such as what kind of patient can benefit most from CIT and the necessity to set inclusion criteria. They also gave some perspectives, including a more efficient delivery mode, reimbursement concerns, and identification of integrated approaches with CIT such as robotics, virtual environments, mental imagery, pharmaceutical manipulations, and cortical stimulation [34]. What made CIT promising to varying clients is the extensive application to patients with cerebral palsy, focal hand dystonia, phantom limb pain, and even cognitive impairments such as aphasia, hemispatial neglect, and memory impairment [35-36].

A recent study conducted by DeBow and colleagues [37] exemplified a flexible 2-way process of translational neurorehabilitation research. Although most major advances in CIT research were made based on human participants, DeBow et al. studied the effects of CIT in rats with intracerebral hemorrhage by combining CIT with environment enrichment and task-specific training [37]. The findings of this study that CIT led to diminished cell death and functional deficits may be indicative of the possibility of applying such an integrated approach to humans in the future.

In conclusion, CIT allows for testable hypotheses in mechanism of dysfunction (learned nonuse) and efficacy after intervention. The research on mechanism of deficit and effectiveness has originated from basic scientific studies on animals and is further expanded through clinical trials on humans. Continued efforts to refine the treatment methods have been made to clarify the critical factors that may account for therapeutic success and may thus maximize the efficiency of applying the intervention. Incorporating evidence-based practice into the clinical setting has been emphasized in recent years. A growing amount of research resource has been devoted to the translation of basic findings to human clinical trials. In the near future, CIT researchers may endeavor to define the critical aspects of this intervention and develop strategies to augment the transfer effects from clinical trials to application in the real world through the ''Blue Highways''—focusing their efforts more on practice-based research.

Possible mechanisms of CIT—accumulation of neural evidence through the translational research map

As the final step of the medical process, rehabilitative medicine focuses on the patient regaining activities of daily life and returning to society. The improvement of behavioral function reflects the recovery of neural injury, the motor compensation, or the consequence of both [38].

Neurorehabilitation scientists tend to seek direct evidence of therapeutic effect coming from changes in the neural system and investigate both the mechanism and contributing factors of neural recovery to develop more effective therapies and then apply them to clinical use.

Neuroplasticity, which is the most well known mechanism of neural recovery, is the alteration of strength on neuronal synaptic connection by environmental stimulation and variation. In a model postulated by Murphy and Corbett [38], training and other enhancing factors result in new circuits being rewired between neurons to cause recovery of behavioral function and compensation by 2 distinct mechanisms. One is homeostatic plasticity, a negative feedback-mediated plasticity that serves to keep network activity at a desired set point [39]. The other is Hebbian plasticity, a positive feedback-mediated plasticity that strengthens and retains properly wired synaptic connections when firing in presynaptic and postsynaptic neurons simultaneously [40]. The re-establishment of the brain area affected by stroke in the early stage (in first 1-4 weeks) is through a homeostatic mechanism that causes structural and functional changes. After the establishment of sensory and motor circuits, Hebbian plasticity is evolved to refine these newly forming circuits. In the following days and weeks, restoration of circuits is actively facilitated by compensatory rewiring or activation in the rest brain area. The functional change of brain areas or the transfer of the sensorimotor signaling from one cortical area to another is considered as brain remapping or brain reorganization [41]. This process suggests not only that the synaptic sensitivity of existing neural connection is altered by inhibitory dynamics but also that the unbalance of bilateral hemispheres is restored gradually after unilateral brain injury.

Taub observed the phenomenon of learned-nonuse behavior in nonhuman primates and induced the actions through constraining with a sling or mitt (forced use). To investigate the mechanism of learned nonuse and how to overcome it, Taub and colleagues depicted a flow chart to integrate behavioral retaining elements of learned nonuse and demonstrated the sequences of these factors [42]. Sunderland and Tuke diversified this chart to raise several compensatory learning factors, including attention, motivation, and perceived sense of effort, which contribute to a patient's reacquisition of unique motor skills [43]. To improve the shortcoming of neuromodulation and movement experience, Wolf further modified the Sunderland-Tuke model with structural and psychosocial considerations [44]. The CIT model has been refined and become more delicate since its inception. Research that enunciates the mechanism underpinning neural recovery after CIT is growing. **Table 2** provides a summary of current evidence for neuroplastic change after CIT organized in accord with the phases of translational research map. The first neural evidence of change in the brain after CIT treatment is the study of *transcranial magnetic stimulation* (*TMS*) reported by Liepert and colleagues in 1998 [45]. This pretest-posttest study in 6 individuals demonstrated that the thumb map enlargement is correlated with motor recovery after CIT. This result was repeated in many subsequent studies that involved more participants [46-47]. Many possible mechanisms of CIT related with motor recovery were evaluated. In addition to the enlargement of the motor map in the unilateral hemisphere, systematic alterations in the brain were also reported. Some studies demonstrated that the "center of gravity" in TMS-associated motor representative map shifts toward the neighboring point after CIT and reflects the neuroplasticity of motor cortex [48]. CIT affects the level of intracortical inhibition, which was indicated by paired-pulse TMS, but the direction of change was inconsistent [49-50]. Although many possible mechanisms of CIT were reported by electromagnetic devices, most studies lacked a well-controlled experimental group needed to reach solid conclusions [51]. However, participants in the study of Boake and colleagues were randomly separated into 2 groups and received CIT or an intensive form of traditional therapy matching the frequency and duration of CIT [21]. The result showed that the thumb map expands in both groups, but no significant differences in map expansion between these 2 groups were found. In another study, a comparison between the CIT group and the usual care control group demonstrated that there was a significant increase of the TMS motor map area in the CIT group compared with the control group during a 4-month period after adjusting for baseline measure [52]. To sum up, there are insufficient data to support the relationship between motor functional recovery and change in the brain.

Table 2. Neural evidence of constraint-induced movement therapy—the process of translation from bench to bedside

Phase of Translational Research	Research Type	Examples
Basic science research	Laboratory experiment	Neurogenesis [60], synapse formation [59] and upregulation of neurotrophic factors[59,60]
Translation to human phase	One-group pretest-posttest design	• TMS: Motor map expansion [45, 46] • fMRI: Inconsistent change of brain activation area or shift in laterality of activation [54-57]
Human clinical research	TMS: randomized control-group pretest -posttest design fMRI: non-randomized control-group pretest-posttest design	• TMS: Significant difference of motor map expansion with usual care control group [52], but not with intensive traditional therapy group [21] • fMRI: Different changing patterns of brain activation area [58]
Translation to patients phase	N/A	N/A
Practice-based research	N/A	N/A
Translation to practice phase	N/A	N/A

TMS: *transcranial magnetic stimulation,* fMRI: functional magnetic resonance imaging, N/A: not applicable.

Brain imaging techniques have been used to improve the study of plastic change in the brain after CIT in the past decade. In 2001, Levy and colleagues first showed an increase of hemispheric activation after CIT treatment in 2 patients examined before and after functional magnetic resonance imaging (fMRI), and this increase was accompanied with regaining motor function [53]. Subsequent studies with more participants repeated the results that the motor recovery after the treatment was correlated with the size change of activation measured by brain imaging, but the patterns were not consistent in each study. For example, Johansen-Berg and colleagues reported that motor gain is correlated with the increased activation in the ipsilesional premotor cortex and bilateral cerebellum, but other studies reported that motor recovery is correlated with increased activation in the contralesional cortex or bilateral cortex [54-55]. In contrast to increased activation, the study of Dong and colleagues demonstrated that activation decreased time-dependently in contralesional motor cortex activation during the treatment [56]. Furthermore, Schaechter and colleagues found a shift in the laterality of fMRI-measured activation toward the contralesional motor cortices after motor recovery [57]. According to these studies, the changing patterns after treatment are too divergent to reach a unified conclusion, and thus it was suggested that additional other factors may be attributed to the response of sensorimotor network to CIT. Compared with well-controlled studies measured by TMS, studies of fMRI are still rare. As we know currently, only one study has explored the differences between CIT treatment and traditional therapies. Lin and colleagues showed increased activation in the bilateral cortex after CIT treatment, especially in the contralesional cortex, whereas decreased activation in the ipsilesional cortex was shown in the traditional intensive therapy group [58]. This study suggested that different therapies have caused various changes in the brain, and more investigations are needed to clarify the mechanism of brain recovery.

In addition to neural evidence from human studies, the evidence at the molecular and cellular

level has been advanced. In 2008, Maier and colleagues reported that growth and synapse formation of corticospinal fiber in rats with spinal cord injury was enhanced by forced use of the impaired limb [59]. This formation is caused by the up-regulation of messenger RNAs, which modulates neuronal outgrowth, cytoskeletal rearrangements, adhesion, and guidance. Further, the effects of CIT on a molecular level in adult rats with stroke were under evaluation. Compared with the control group, the ischemia group with CIT treatment showed improvement in neurogenesis and expression of stromal cell-derived factor-1 (SDF-1), a cytokine involved in proliferation and differentiation of neural progenitor/stem cells [60]. Although investigations of neuronal change on molecular and cellular level are scarce, these studies provided the evidence to support that behavioral improvement is based on neuronal regeneration involving neurogenesis, synapse formation, and upregulation of neurotrophic factors.

Even though Taub observed behavioral features in nonhuman primates, direct neural evidence of CIT was obtained based on human research. This indicates the fact that CIT techniques have been applied to patients with brain injury despite the lack of sufficient neural evidence for how this family of treatment techniques may work in restoring brain function. There may be several reasons. At first, researchers did not engage in studying regeneration in the adult brain because of the theory that was inherited from Cajal [61-62]. Scientists became interested in estimating regeneration in the adult brain after Gould and colleagues reported neurogenesis in the hippocampus and neocortex in the adult monkey [63-64]. Second, the collection of neural evidence was hindered because electromagnetic and brain imaging devices were not available for large-scale animal or clinical trials until the past decade [65-66]. Third, learning-based neurorehabilitation cannot be totally simulated by animal models because the learning mechanism involves many high-level cognitive functions related to culture, language, and habits, factors that may affect the reproducibility of animal models in clinical research.

In keeping with the advances in restorative neurosciences, it is important to study the behavioral effects and neural evidence of rehabilitation therapies in humans. Neural evidence may support the changes in the brain after treatment and proves that the improvement of behavioral function after brain injury is based on neural recovery rather than completely depending on behavioral compensation. In addition, through understanding influencing factors such as site of brain lesion, integrity of the white matter, brain network changes, and training effects through brain imaging, therapists may design personalized treatment programs for patients with various neurological disorders [67]. Another application of neural evidence is to predict treatment response and such data may be useful in patient screening. For example, the laterality index and motor cortex function are both predictors used to forecast the gain of motor function after rehabilitation treatment [68]. Consequently, brain imaging is regarded as a biomarker for understanding the pattern and process of recovery from brain injury and may guide the development of personalized rehabilitative therapies [69-70].

Discussion

Although the developments of rehabilitative therapies and new drugs are both following the map of translational research to apply findings of basic science to clinical applications, many differences exist between them. For example: (1) Since the investigation of brain function has sprouted in recent decades, the application of translational research on rehabilitative medicine is slower than the development of new drugs; (2) Because the effect of learning-based rehabilitative medicine is accumulative and noninvasive, clinical research of leaning-based rehabilitative medicine does not emphasize serious toxic and side effect tests; (3) The development of rehabilitative therapy does not require full understanding about the therapeutic mechanism before it is applied in clinical use; in contrast, therapies are advanced to investigate the therapeutic mechanism after observing clinical effectiveness; (4) Rehabilitative medicine is focused on the functional outcome related to personal occupation, so the results of animal model experiments cannot be used to predict its measurable outcomes in clinical research.

More rigorous work is needed to test the efficacy of new therapies in comparison with conventional intervention in order to advance comparative efficacy research in neurorehabilitation. Such endeavors are important and timely

to translate clinical research to everyday clinical practice of neurologic rehabilitation. As indicated above, CIT has prominent effects on motor recovery in clinical research, but it did require much time to take effect. Modified forms of CIT have been proposed to refine the standard protocol for improved feasibility and clinical utility [28, 71-72]. The CIT concepts and applications in various forms have heated research of practice implications derived from contemporary clinical neurosciences. For example, the theory of the mirror neuron system addressed by Rizzolatti suggested that certain groups of neurons—mirror neurons—are activated when observing meaningful action and thus may be important in motor learning and motor imitation [73-74]. Based on this theory, mental imagery or motor training with a mirror, termed "mirror therapy," is applied in the clinic to assist motor recovery in brain injury patients [75-76]. By means of translational research, innovative applications of growing therapies based on basic research findings may be facilitated. As an example, the concept of replacing injured brain areas with new neural cells to repair damaged brain function has bourgeoned in recent years with the accompanying advances in stem cell study [77]. After serial experiments in animal models, many clinical trials of cell transplantation therapy have begun to explore different aspects of treatment, such as cell dose, time window, and side effects [78-79]. Some of these clinical studies demonstrated good clinical outcome after cell transplantation [80]. In the future, a combination of stem cell therapy and learning-based neurorehabilitative therapy may be a more effective way to facilitate brain recovery. In addition, brain and cognitive reserve, the concept derived from environmental enrichment, is described as the resilience of mind responding to neuropathological brain damage [81]. Environmental enrichment, which has been done to give more opportunities for physical activity, learning, and social interaction, may produce structural and functional changes of the brain as well as accelerate the rate of neurogenesis in adults and neurodegeneration animal models [82-83]. Human aging, education, life style, leisure activity, and occupation are factors found to be related to cognitive functioning levels in several studies, and the cognitive reserve is also suggested to reflect the persistence of early differences in cognitive function rather than differential rates of age-associated cognitive declines [84-85]. It was reported that brain and cognitive reserve strongly support the idea—"prehabiliatation" in neural and cognitive levels; it means that convalescence of brain damage and competence in maintenance activities of daily life can be achieved with better modulation of these crucial factors.

Conclusion

It may take as long as 20 years, or longer, for a theoretical basis for a new therapy to be conceived to the intended therapy and then to be implemented in regular health care [86-87]. Translational research serves as a freeway linkage between basic research and clinical practice to help facilitate the accessibility between the two. To consolidate the development of translational neurorehabilitation, several issues warrant considerations: (1) Because several models of neurodegeneration and psychiatric diseases have been developed over the years, neurorehabilitation researchers should apply these models to study the theory-driven interventions alone or in combination with other therapies (eg, binding rehabilitation to pharmaceutical interventions, stem cell therapies, environmental control, etc.); (2) Neurorehabilitation researchers should proactively translate basic research results into first-in-human research and study both beneficial and adverse effects. (3) Neurorehabilitation researchers should also make use of functional brain imaging techniques to study plastic change in the brain during and after rehabilitative therapies and project the dose-response relations. (4) Patient-reported outcomes should be evaluated along with physiologic and physical responses to capture a more comprehensive picture of the impact of neurorehabilitation on clients' and caregivers' quality of life [88].

Efforts directed toward these lines of inquiry may allow practitioners to sketch more personalized rehabilitation programs based on current best evidence of basic and clinical neurosciences. Evaluations for the performance of clinical applications will feedback in turn to the advances of new hypotheses tenable for scientific scrutiny.

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