CI Therapy: A Method for Harnessing Neuroplastic Changes to Improve Rehabilitation after Damage to the Brain

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Abstract. Constraint-Induced Movement (CI) therapy has been successfully implemented for treating motor deficit resulting from a variety of previously intractable neurological conditions such as traumatic brain injury. CI therapy's efficacy can be attributed to two interrelated mechanisms: overcoming "learned nonuse" and neuroplasticity. Voxel-based morphometry (VBM) analyses have demonstrated that CI therapy produces lasting *structural* changes to the human brain. Patients that received full CI therapy demonstrated profuse grey matter increases in sensory and motor areas and hippocampus, whereas those who received only intensive motor practice did not. The magnitude of the observed structural changes was correlated with the extent to which the patient regained use of the impaired arm for daily activities. These findings demonstrate that the two mechanisms believed to underlie improvement from CI therapy, overcoming "learned nonuse" and neuroplasticity, act synergistically. Therefore, a bidirectional approach to treating brain injury, one that targets both brain and behavior, is suggested.

1 Introduction

Traumatic brain injury (TBI) is a leading cause of death and lifelong disability among children and young adults in the United States [1]. The number of young Americans experiencing TBI has significantly increased in recent years as a result of combat in Iraq and Afghanistan. According to the Joint Theater Trauma Registry, compiled by the U.S. Army Institute of Surgical Research, over 22% of the soldiers treated in U.S. military hospitals between 2003 and 2005 sustained injuries to the head, neck and face [2]. Approximately 50% of those injured in blast suffered a TBI. Among Walter Reed admissions of war fighters, 54% sustained moderate-severe brain injury [3,4]. Among civilians as well as military personnel, an estimated 5.3 million men, women and children are living with permanent TBI-related disability in the United States today [5]. These disabilities, including movement impairments, often permanently alter a person's vocational capabilities and have profound effects on their lives. The TBI population consists predominately of young males with a potential for employment. Motor disability, combined with cognitive and behavioral deficits, results in poor

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post-injury employment outcome [6-8]. According to a 1985 study, the annual economic burden of TBI in the United States was approximately $37.8 billion [9]. With rising healthcare costs since that time, these figures have undoubtedly grown substantially. Effective therapeutic interventions for TBI survivors could therefore dramatically decrease TBI's cost to society by increasing quality of life for TBI survivors and their families as well as reducing its economic burden.

A new class of therapy, termed Constraint-induced Movement therapy (CI therapy), was developed to substantially reduce the incapacitating motor deficit and to greatly increase use of an impaired extremity in the life setting following neurological damage. CI therapy was derived from basic behavioral neuroscience research with primates by Taub and colleagues. When a single forelimb is deafferented in a monkey, the animal does not make use of it in the free situation [10,11], but it can be induced to use the deafferented extremity by restricting movement of the intact limb and operant training procedures (e.g. conditioned response training, shaping progressive improvements in movement) [12-14]. Similar training principals were later successfully applied to humans with chronic hemiparesis resulting from stroke; CI therapy has demonstrated efficacy in multiple studies using between- and within-subject controls, placebo controls, and convergent measures from multiple domains [15-20]. A recent multi-site randomized clinical trial (EXCITE) with subacute patients 3-9 months post-stroke reported positive results [19]. Although originally designed to treat stroke patients, CI therapy has been successfully implemented for treating a variety of previously intractable neurological conditions including: TBI [21,22] multiple sclerosis (MS) [23], cerebral palsy [24], and juvenile hemispherectomy [24] with similar clinical outcomes. Although CI therapy does not restore normal movement ability to the arm, individuals who receive the therapy are often able to regain substantially improved use of the formerly hemiparetic arm for many activities of daily living. Its effectiveness may be attributed to two independent but interrelated processes: overcoming learned nonuse of the extremity and altering the structure and function of the human brain.

After any substantial neurological injury, there is a period of suppressed central nervous system activity and corresponding decrease in motor function. During this period, an operant learning process takes place that involves behaviorally reinforced suppression of attempts to move an impaired limb. As a result, individuals with motor deficit demonstrate greatly reduced movement of the affected extremity despite a gradual spontaneous recovery of at least some of the lost function (i.e. learned nonuse) [15, 25]. Almost 90% of TBI patients with motor deficit evaluated in Taub's laboratory exhibited considerably greater use of one arm than the other. Although the brain damage associated with TBI is typically bilateral, damage to the motor network may be greater in one hemisphere than in the other. We believe that this motor advantage of one arm compared to the other is accentuated because the learned nonuse mechanism is based on the greater reward (i.e., success) produced by use of the more effective arm even though the advantage initially may be small. This further increases its use relative to the less used arm, and may result in contractions of the cortical representation zone for the less used arm and increased cortical space devoted to use of the more frequently used extremity [26-30]. This would make the more used extremity progressively easier to use and it would become increasingly difficult for the patient to use the less frequently used arm. The process may be described as a vicious spiral downward for the less used arm that results in the appearance of relative hemiparesis despite bilateral damage to the brain (we have observed this same phenomenon in patients with progressive MS [23], where the neurological damage is also bilateral).

2 Method: CI Therapy

CI therapy consists of three main elements with demonstrated efficacy for overcoming learned nonuse [17, 31]. One component is intensive training of the more affected arm for three hours per day for ten consecutive weekdays. In some respects, this training is similar to what would be obtained through traditional physical or occupational therapy; however, there are several important distinctions: CI therapy focuses entirely on training the more affected extremity, incorporates "shaping" procedures (a desired movement goal is approached in small steps, by successive approximations and continuous feedback), and the duration and intensity of training is greater than is typically carried out in other more traditional forms of therapy. A second component is prolonged restraint of the less affected upper extremity for a target 90% of waking hours to encourage increased use of the more impaired arm. The third and final component is a "transfer package" of behavioral techniques designed to facilitate transfer of therapeutic gains achieved in the laboratory/clinic to real world activities. The transfer package consists of a behavioral contract, monitoring of life situation more-affected arm use by daily administration of the Motor Activity Log (a structured interview concerning the amount and quality of more affected arm use for 30 activities of daily living carried out in the life situation), and problem solving with a therapist to overcome perceived barriers to using the extremity, among several other elements. The transfer package has been shown to be a critical component of the therapy; if absent from the intervention, improvements in spontaneous real world arm use are reduced approximately threefold [32].

3 Results: Neuroimaging Studies Involving CI Therapy

In addition to overcoming learned nonuse, the efficacy of CI therapy may be attributed to a second, related mechanism: neuroplasticity. Decreases in afferent input, such as reduced movement following insult to the brain, have been associated with contraction of the cortical representation zones of the affected extremity [26-30]. Conversely, CI therapy has been shown to increase the cortical representations of affected upper extremity muscles within ipsilesional primary motor cortex in stroke patients [26, 27, 33]. Furthermore, increased recruitment of motor cortex paralleled improvements in amount and quality of daily arm use [27]. CI therapy has been shown to produce "functional" alterations in the excitability, rate of metabolism, and blood flow in ipsilesional brain areas associated with the more affected arm [34, 35]. Other investigators have demonstrated CI therapy-induced functional reorganization in contralesional areas of the brain [36,37], presumably reflecting reorganization of function in the less affected hemisphere. However, a weakness of these studies is that they were limited to using imaging techniques such as transcranial magnetic stimulation [26, 27, 33-35], positron emission tomography [34], and fMRI [35] which record alterations in excitability, rate of metabolism, or blood flow, all of which can fluctuate on a moment-to-moment basis.

More recently, results from a voxel-based morphometry (VBM) study demonstrated that CI therapy produces lasting structural changes to the human brain in addition to the aforementioned physiological changes in brain function [32]. Chronic stroke patients enrolled in a recent randomized controlled trial of CI therapy were assigned to receive either intensive motor practice only (the first component of CI therapy discussed above) or full CI therapy involving all three components including the transfer package. Longitudinal VBM was performed on structural magnetic resonance imaging (MRI) scans obtained immediately before and after patients received therapy to determine structural changes in grey matter. The group receiving all components of CI therapy exhibited far greater improvement in use of the more affected arm in the life situation than the group that received only intensive motor practice. Increases in grey matter paralleled improvements in spontaneous use of the more impaired arm for activities of daily living. The CI therapy group exhibited profuse increases in grey matter in sensory and motor cortices both contralateral and ipsilateral to the affected arm, as well as in bilateral hippocampi. These changes in grey matter were restricted to cortical areas typically involved in motor control of the arm/hand (and not adjacent areas of motor cortex); they may reflect synaptogenesis [38-43], gliosis [44, 45], angiogenesis [46, 47], and possibly neurogenesis [48-51]. The group that received only intensive motor practice failed to exhibit significant grey matter increases. Furthermore, the magnitude of the observed structural changes was correlated with the extent to which the patient regained use of the impaired arm for daily activities. This study demonstrates that real-world arm use is a critical component driving rehabilitation-induced neuroplasticity.

4 Discussion

Although there are several possible explanations for these data, one hypothesis is that neuroplastic changes are sensitive to the behavioral relevance of motor tasks, such as use of the more affected arm for activities of daily living at home encouraged by the transfer package. A similar phenomenon has been demonstrated by Jenkins, Merzenich and colleagues in the sensory system of monkeys [52]. Their studies showed that repetitive “behaviorally relevant” sensory stimulation resulted in plastic expansion of the cortical representations of stimulated digits whereas equal amounts of sensory stimulation that was not behaviorally relevant did not significantly alter these representation zones (behavioral relevance was provided by requiring the monkey to make an accurate discrimination response to differences in the tactile stimulation to obtain food or liquid reward). Alternatively, motor tasks performed in the home may be more complex than the structured tasks used for motor training in the laboratory and may involve the simultaneous coordination of more muscle groups and therefore produce a greater neuroplastic response [39, 40, 46, 53-55]. Empirical investigation could further elucidate the mechanisms by which an individual’s behavior influences brain structure and function.

TBI involves different neuropathology than does stroke. The stretching and shearing associated with brain trauma causes a misalignment in the cytoskeleton followed by accumulation of intracellular structures and swelling that can cause a separation of the axon [56]. It is therefore unclear whether the neuroplastic response of TBI patients to CI therapy differs from that demonstrated within a stroke population. However, TBI patients treated with CI therapy show clinical improvements equivalent to those observed in the stroke population [21, 22]. One might make the assumption that behavioral changes are reflective of changes in brain structure or function. Therefore, it is highly possible that neuroplastic mechanisms are operating in the brains of TBI patients treated with CI therapy that are similar to those shown to occur in patients with stroke.

5 Conclusion

What is currently known regarding structural brain changes after CI therapy has substantial implications for rehabilitation. The aforementioned data demonstrates that the two mechanisms believed to underlie improvement from CI therapy, overcoming learned nonuse and neuroplasticity, act synergistically. Although the brain produces movement, purposeful movement can have an equally profound reciprocal effect on brain structure and can be harnessed for therapeutic effect. The magnitude of structural brain change and therapeutic effect appears to depend on the nature and extent of the change in behavior, however. Fundamental behavioral change involving incorporation of the impaired extremity into activities of daily living was necessary to drive neuroplastic reorganization of brain, whereas intensive movement training alone was insufficient. In summary, brain structure/function and the behavior of the individual appear to be interdependent processes that drive therapeutic improvement following insult to the brain. Therefore, a bidirectional approach to treating brain injury, one that targets both brain and behavior, is suggested.

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