Constraint-Induced Movement Therapy: A Family of Neurorehabilitation Treatments that Harnesses the Plasticity of the Central Nervous System

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Abstract

Constraint-Induced Movement Therapy or CI Therapy is an approach to physical rehabilitation elaborated from basic neuroscience and behavioral research with primates. The application of the CI therapy protocol to humans began with the upper-extremity after stroke and was then modified and extended to cerebral palsy in young children, traumatic brain injury, and multiple sclerosis. A form of CI therapy was developed for the lower extremities and has been used effectively after stroke, spinal cord injury, fractured hip, multiple sclerosis, and cerebral palsy. Adaptations of the CI therapy paradigm have also been developed for aphasia (CI Aphasia Therapy or CIAT), focal hand dystonia in musicians, and phantom limb pain. The range of these applications indicates that CI therapy is not only a treatment for stroke, which is its most common application, but for overcoming learned nonuse in general, a phenomenon which manifests as excess disability after different types of CNS injury which until now have been largely refractory to treatment. CI therapy in all of its forms consists of four major components: 1) intensive training of an impaired function for several hours a day for multiple days, 2) training by the behavioral technique termed shaping, 3) a set of behavioral techniques, the transfer package, designed to transfer gains from the treatment setting to daily activities in the life situation, and 4) "constraining" or discouraging compensatory patterns of movement developed in the early post-injury period to substitute for loss of function. CI therapy for the upper-extremity in adults and children has been shown to produce an increase in the volume of grey matter in motor areas of the brain and there is evidence that CI Aphasia Therapy has a similar effect in language-related regions.

Key words: Constraint-Induced Movement Therapy, Constraint-Induced Aphasia Therapy, rehabilitation, hemiparesis, aphasia, stroke, cerebral palsy, multiple sclerosis, traumatic brain injury, spinal cord injury

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Recovery of Function after Unilateral Forelimb Deafferentation in Primates

When somatic sensation is surgically abolished from a single forelimb in monkeys by severing all dorsal spinal nerve roots innervating that limb, the animal does not make use of it in the free situation [31, 32, 39, 56, 104]. This is the case even though the motor outflow over the ventral roots remains uninterrupted. However, monkeys can be induced to use the deafferented extremity by restricting movement of the intact limb [32, 82, 83]. The monkey may not have used the affected extremity for several years, but the application of this simple technique results in a striking conversion of the useless forelimb into a limb that is used for a wide variety of purposes [79, 80]. The movements are clumsy since somatic sensation has been abolished, but they are extensive and effective. This may be characterized as a substantial rehabilitation of movement, though the term is not usually applied to monkeys. If the restraint device is left in place for a period of 1 week or more, the newly developed ability to use the limb continues when the restraint device is removed and permanent, persisting for the animal's lifetime.

Training procedures are another means of overcoming the inability to use a single deafferented forelimb in primates [31, 32, 78-83, 86, 87, 101]. Transfer from the experimental to the life situation was never observed when using discrete trial conditioned response techniques to train limb use. However, when shaping was employed, there was substantial improvement in the motor ability of the deafferented limb in the life situation [78, 79, 83, 87]. Shaping is an operant training method in which a desired motor or behavioral objective is approached in small steps, by "successive approximations", so that the improvement required for successful

Constraint-Induced Movement Therapy: Neurorehabilitative Therapien machen sich die Plastizität des Gehirns zunutze

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Abstract

Constraint-Induced Movement Therapy (CI) ist ein Ansatz in der Neurorehabilitation, der sich aus der neurowissenschaftlichen Grundlagenforschung und verhaltensbiologischen Untersuchungen an Primaten entwickelte. Das CI-Verfahren wurde beim Menschen zuerst in der Rehabilitation einer Armlähmung nach Schlaganfall eingesetzt und später für die Indikationen frühkindliche Zerebralparese, Schädelhirntrauma und Multiple Sklerose modifiziert und ergänzt. Auch für die untere Extremität wurde eine spezielle Form der CI-Therapie entwickelt und erfolgreich nach Schlaganfall, Rückenmarksverletzungen, Hüftfrakturen, Multipler Sklerose und Zerebralparese eingesetzt. Adaptionen der CI-Therapie wurden für die Aphasietherapie (CI Aphasia Therapy, CIAT), die fokale Dystonie der Hand bei Musikern und den Phantomschmerz konzipiert. Die große Bandbreite dieser Indikationen spricht dafür, dass die CI-Therapie nicht nur in der Schlaganfallbehandlung, dem derzeit häufigsten Einsatzgebiet, anwendbarbar ist. Sie lässt sich auch ganz allgemein nutzen, um den erlernten Nichtgebrauch zu überwinden – ein Phänomen, das als »excess disability« (übermäßige Behinderung) nach verschiedenen Schädigungen des Gehirns auftreten kann, die bisher als weitgehend therapierefraktär gelten. Alle Formen der CI-Therapie beinhalten vier Hauptkomponenten: (1) Intensives Training einer gestörten Funktion über mehrere Stunden über einen längeren Zeitraum; (2) Training mit einer Verhaltenstechnik, die als »shaping« (Modellierung) bezeichnet wird; (3) ein Paket von Verhaltenstechniken, das »transfer package«, das die in der Therapie erzielten Funktionsverbesserungen auf die »activities of daily living« (ADL) im Alltag übertragen soll und (4) die Hemmung und »Abschreckung« kompensatorischer Bewegungsmuster, die in der frühen posttraumatischen Phase entwickelt werden, um die verlorene Funktion zu ersetzen. Es ist erwiesen, dass CI-Therapie der oberen Extremität bei Kindern und Erwachsenen zu einem Zuwachs an grauer Substanz in motorischen Arealen des Gehirns führt und es gibt deutliche Hinweise darauf, dass dasselbe für sprachrelevante Regionen bei der CI-Aphasietherapie gilt.

Key words: Constrained-Induced Movement Therapy, Constrained-Induced Aphasia Therapy, Rehabilitation, Hemiparese, Aphasie, Schlaganfall, Zerebralparese, Multiple Sklerose, Schädelhirntrauma, Rückenmarksverletzung

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performance at any one point in the training is small [53, 61, 70, 72, 73, 84]. The actions shaped included (a) pointing at visual targets [87] and (b) thumb-forefinger prehension in juveniles deafferented on day of birth [91] and prenatally by intra-uterine surgery, [92] who had not exhibited any prehension previously. In both cases, shaping produced an almost complete reversal of the prior motor disability, which progressed from total absence of the target behavior to good (although not normal) performance.

During the course of this century, several other investigators have found that a behavioral technique could be employed in animals to substantially improve a motor deficit resulting from neurological damage [11, 38, 59, 102]. However, none of these observations was embedded in a formal theoretical context that permitted prediction nor was the generality of the mechanisms recognized. Consequently, these findings remained a set of disconnected observations that received little attention.

Initial Applications of Primate Model to Rehabilitation of Paretic Arm Use after Stroke in Humans

The initial studies of the application of CI therapy to humans were carried out by Ince [27] and Halberstam, Zaretsky, Brucker, and Guttman [25]. Ince transferred the conditioned response techniques used with the deafferented monkeys that he had observed in Taub' s laboratory [81, 82] directly to the rehabilitation of movement of the paretic upper extremity of 3 patients with chronic stroke. He secured the less-affected upper extremity of the patients to the arm of a chair, while asking the patients to flex their more-affected arm at the sound of a buzzer to avoid a mild electric shock, as in the primate experiment he observed. The motor status of two of the patients did not change; the third patient, however improved substantially in the training and life situations [27]. Halberstam et al. [25], from a nearby institution, used a similar treatment protocol with a sample of 20 elderly patients with stroke and 20 age-matched controls. The treatment group was asked to either flex their more-affected arm or to make a lateral movement at the elbow at the onset of a tone to avoid electric shock; the less-affected arm was not tied down. Most of the patients in the treatment group increased the amplitude of their movements in the two conditioned response tasks; some showed very large improvements [25]. There was no report of whether this improvement transferred to the life situation.

Steven Wolf and coworkers [60, 117] applied the less-affected limb restraint portion, but not the more-affected limb training component, of the CI therapy protocol described by Taub [80] to the rehabilitation of movement in persons with a chronic upper mild/moderate extremity hemiparesis. The patients were asked to wear a sling on the less-affected arm all day for 2 weeks, except during a half-hour exercise period and sleeping hours. The patients demonstrated significant but small improvements in speed or force of movement on 19 of 21 tasks on the Wolf Motor Function Test (WMFT), a laboratory test involving simple upper extremity movements and performance of some tasks. There was no report of whether the improvements transferred to the life situation. Though the effect size was small ($d' = 0.2$), it was reliable. The results appeared promising, especially since training had not been used and there was some question of compliance by some patients with the instruction to wear the sling for most of waking hours during the intervention period. This type of intervention involving only use of a restraint device is termed *Forced Use* therapy; it is not CI therapy since it consists of only one of the four primary components of CI therapy.

Impairment	Shoulder	Elbow	Wrist	Fingers	Thumb
Grade 2 (MAL < 2.5 for AS & HW scales)	Flexion ≥ 45° and abduction ≥ 45°	Extension ≥ 20° from a 90° flexed starting position	Extension ≥ 20° from a fully flexed starting position	Extension of all MCP and IP (either PIP or DIP) joints ≥ 10°*	Extension or abduction of thumb ≥ 10°
Grade 3* (MAL < 2.5 for AS & HW scales)	Flexion ≥ 45° and abduction ≥ 45°	Extension ≥ 20° from a 90° flexed starting position	Extension ≥ 10° from a fully flexed starting position	Extension ≥ 10° MCP and IP (either PIP or DIP) joints of at least 2 fingers †	Extension or abduction of thumb ≥ 10°
Grade 4† (MAL < 2.5 for AS & HW scales)	Flexion ≥ 45° and abduction ≥ 45°	Extension ≥ 20° from a 90° flexed starting position	Extension ≥ 10° from a fully flexed starting position	Extension of at least 2 fingers > 0° and < 10° †	Extension or abduction of thumb ≥ 10°
Grade 5 (LF-MAL < 2.5 for AS & HW scales)	At least *one* of the following: Flexion ≥ 30° abduction ≥ 30° scaption ≥ 30°	Initiation ‡ of both flexion and extension	Must be able to *either* initiate‡ extension of the wrist *or* initiate extension of one digit		

Table 1: Stratification of Severity of Impairment: Active Range of Motion and Mean MAL Score Criteria

MAL indicates Motor Activity Log; AS & HW scales indicate Amount and How Well Scales of the MAL; MCP indicates metacarpophalangeal joints; IP indicates interphalangeal joints; PIP indicates proximal interphalangeal joints; DIP indicates distal interphalangeal joints; LF-MAL indicates Lower Functioning Motor Activity Log.

Each movement must be repeated 3 times in 1 minute. Grade 6 patients would fall below the minimum Grade 5 criteria.
* Informally assessed when picking up and dropping a tennis ball.
† Informally assessed when picking up and dropping a washcloth.
‡ Initiation is defined for the purposes of criteria as minimal movement (i. e., below the level that can be measured reliably by goniometer).

Demonstration of Efficacy of CI Therapy at University of Alabama at Birmingham (UAB)

Taub et al. [90] applied both the affected arm training and contralateral arm restraint portions of the CI therapy protocol and also a set of behavioral techniques termed the *transfer package* [54, 97–99] to the rehabilitation of persons with a chronic upper extremity hemiparesis in a study that employed an attention-placebo control group and emphasized transfer of therapeutic gains in the laboratory to the life situation. Patients with chronic stroke were selected as subjects for this study because according to the research literature at the time [2, 62, 103], and clinical experience, spontaneous motor recovery was thought to reach a plateau within 1 year after stroke. There was no evidence that any treatment could produce further recovery of function after that time. Therefore, any marked improvement in the motor function of individuals with chronic stroke would be of particular therapeutic significance. After a long-standing plateau, the probability would be very low that an abrupt, large improvement in motor ability could be due to spontaneous recovery.

Four treatment subjects signed a behavioral contract in which they agreed to wear a sling on their less-affected arm for 90% of waking hours for 14 days. On the 10 weekdays during that period, the treatment subjects received 6 (later reduced to three) hours of supervised task practice using their more-affected arm (e.g., eating lunch, throwing a ball, playing dominoes, Chinese checkers or card games, writing, pushing a broom, using the Purdue Pegboard and Minnesota Rate of Manipulation Test) interspersed with one hour of rest. Five control subjects were told they had much greater movement in their more-affected limb than they were exhibiting, were led through a series of passive movement exercises in the treatment center, and were given passive movement exercises to perform at home. All experimental and control subjects were at least 1 year post-stroke ($M = 4.4$ yr). Their motor deficit could be characterized as mild/moderate or Grade 2 in the UAB system of classifying motor deficit based on active range of motion at each of the upper extremity joints (see Table 1). Treatment efficacy was evaluated by the WMFT [55, 90, 117, 118], the Arm Motor Ability Test (AMAT) [34, 49], and the Motor Activity Log (MAL) [90] a structured scripted interview with established reliability and validity [109–111] tracking arm use in a number of important activities of daily living (ADL). On the MAL, the treatment group showed a large increase in real-world arm use over the 2-week period and no decrease in retention of the treatment gain in real-world use when tested 2 years after treatment. In other experiments, we have found a 20% decrement in retention over a 2-year post-treatment period in patients with a similar (mild/moderate) deficit as the patients in this experiment. The control subjects exhibited no change or a decline in real-world arm use over the 2-week treatment period. The treatment group also demonstrated a significant increase in motor ability as measured by both laboratory motor tests (WMFT, AMAT) over the treatment period, whereas the control subjects showed no change or a decline in arm motor ability

These results have since been confirmed in an experiment using shaping [84] of more-affected arm movements instead of task practice and less-affected arm constraint [97]. This experiment also had a larger sample

($N = 41$) and a more credible control procedure than in the first study. The shaping procedure involved requiring that improvements in performance be made in small steps (successive approximations), providing explicit feedback and verbal reinforcement for small improvements in task performance, and selecting tasks that were tailored to address the motor deficits of the individual patient [84, 93]. Modeling, prompting, and cuing of task performance were also used. The control group was designed to control for the duration and intensity of the therapist-patient interaction and the duration and intensity of the therapeutic activities. The control procedure was a general fitness program in which subjects performed strength, balance, and stamina training exercises, engaged in games that stimulated cognitive activity, and practiced relaxation skills for 10 days. Both experimental and control subjects were at least 1-year post-stroke ($M = 4.5$ yr) and exceeded the minimum motor criterion used in the first experiment prior to entry into the study. In addition, all subjects exhibited a substantial lack of spontaneous use of their more-affected arm in their daily life, as defined by a score of less than 2.5 on the MAL (less than half as much use of the more impaired arm compared to before the stroke in the life situation). The motor deficit and amount of arm use of subjects in the two groups prior to treatment was not significantly different. As in the first experiment, the treatment group demonstrated a significant increase in motor ability on the WMFT and a large increase in real-world arm use over the course of the intervention, whereas the control subjects did not. Control subjects' answers to an expectancy and self-efficacy questionnaire about their expectations for rehabilitation prior to the control intervention and their reported increase in quality of life after the intervention, as measured by the SF-36 [113], suggested that they found the control intervention to be credible.

Differential Effect on Actual Life Situation Use vs. Best Performance Made on Request in the Laboratory

Several hundred patients with chronic stroke with mild/moderate motor deficits (Grade 2; an estimated 25 % to 35 % of the chronic stroke population) have been given upper extremity CI therapy to date in this laboratory. For the WMFT, a laboratory motor function test in which the tester requests that subjects make the best movements of which they are capable in 15 timed tasks, the mean pre- to post-treatment effect size (ES) was $d' = .9$; the mean ES (d') for the MAL, which records spontaneous use of the more-affected arm in ADL in the life situation, was 3.3. The much larger ES for the MAL than for the WMFT indicates that CI therapy has its greatest effect on increasing the actual amount of use of a more-affected upper extremity in the real-world setting, though the improvement in quality of movement as indexed by the WMFT is still substantial. In the meta-analysis literature, an ES (d') of 0.2 is considered small, a 0.4 – 0.6 ES is moderate, while ESs of 0.8 and above are large [12]. Thus, the ES of CI therapy for real-world outcome in patients with chronic stroke from the upper quartile of motor functioning is extremely large. This differential effect would appear to be due to the ability of CI therapy to overcome the "learned nonuse" that frequently depresses the spontaneous use of a more-affected arm after CNS damage.

Components of CI Therapy

The upper-extremity CI therapy protocol, as practiced in the UAB laboratory, consists of four basic components [77, 97, 99]: 1) intensive training of the more-affected arm for multiple days; 2) training with a behavioral technique termed shaping; 3) the transfer package (TP), a set of behavioral techniques designed to facilitate transfer of therapeutic gains from the treatment setting to daily life; and 4) discouraging compensatory use of the less-affected arm for a target of 90 % of waking hours for the entire treatment period by using a restraining device, originally a sling and more recently a heavily padded protective safety mitt; the amount of time the device is worn is recorded by a timer inserted in the device.

Shaping is a training method in which a motor or behavioral objective is approached in small steps by "successive approximations" (i. e., a task is gradually made more difficult with respect to a participant's motor capabilities). Its principles were explicitly formulated by Skinner [72, 73] and they have been applied to the rehabilitation of movement in this laboratory [84, 90]. For rehabilitation, shaping involves a) providing immediate and very frequent feedback concerning improvements in the quality of movement, b) selecting tasks that are tailored to address the motor deficits of individual participants, c) modeling, prompting, and cuing of task performance, and d) systematically increasing the difficulty level of the task performed in small steps when improvement is present for a period of time. In this laboratory shaping has two distinct levels. The first level is directed toward improving the speed and quality of movement from trial to trial within a task with frequent feedback and encouragement being given. The second level involves introducing a new task that is similar to but more difficult than the one being used when motor performance improves to the point where the therapist feels that the new task can be accomplished by the participant (e. g., Task 1 – picking up and moving as many standard checker game counters as possible in 30 sec, followed after skill acquisition by Task 2 – use of slick round glass marbles). When the emphasis is on the between-level task modification process, the procedure is sometimes referred to as "adaptive task practice" [115]. The procedure employed here involves use of both levels of shaping but focuses more attention on improving within-level task performance.

The transfer package (TP) consists of a set of techniques in common use in the behavior analysis field for the treatment of a variety of conditions for such problems as medication adherence, adherence to an at-home exercise regimen for low back pain, drug addiction treatment, addiction relapse prevention, and alteration of autism spectrum behaviors; but they have not been used systematically in rehabilitation. The TP techniques used here are: behavioral contracts, daily home diary, daily administration of the Motor Activity Log to track amount and quality of use of the more-affected arm in 30 important ADL, problem solving to overcome perceived barriers to more-affected arm use in ADL performance, written assignment during treatment of practice at home both of tasks carried out in the laboratory and use of the more-affected arm in specified ADL, post-treatment home skill practice assignments, weekly telephone calls for the first month after laboratory treatment in which the MAL is given and problem solving carried out.

Procedures of the Transfer Package

■ *Behavioral Contract.*
At the outset of treatment, the therapist negotiates a contract with the participant and separately with the caregiver, if one is available, in which they agree that the participant will use or try to use the more impaired arm as much as possible outside the laboratory and wear the restraint device whenever it is safe for up to 90% of waking hours. Specific activities during which the participant will use or try to use the more impaired arm are discussed and written down. At the end of this process, the negotiated document is signed by the patient, the therapist, and a witness to emphasize the character of the document as a contract.

■ *Daily home diary.*
During treatment, the participants record how much they have used the more-affected arm for the activities specified in the behavioral contract. The diary is kept for the part of the day spent outside the laboratory and is reviewed in detail each morning with the therapist.

■ *Daily administration of the Motor Activity Log (MAL).*
The MAL collects information about use of the more-affected arm in 30 important and commonly performed ADL. The daily repetition of "how well" participants complete the activities in this detailed report is probed and verified in a number of ways [108] and serves to keep participants' attention on use of the more-affected arm outside the laboratory.

■ *Problem Solving.*
Daily during treatment and in four weekly phone contacts following treatment, the therapist helps participants to think through any barriers to using their more-impaired arm and ways to overcome them. For example, if a participant is concerned about spilling liquid from a glass, the therapist may suggest only filling the glass half way. If a participant is embarrassed by clumsiness in use of the more-affected arm in feeding themselves in a restaurant (many of the UAB patients are from out-of-town), the therapist may suggest eating in the hotel room.

■ *Home skill assignments during treatment.*
Participants are assigned on a written check-off sheet 10 specific ADL tasks in which the more-affected arm should be used, with 5 easy tasks for that participant and 5 more difficult (e.g., carrying the mail, sorting the mail, opening the curtains, making the bed, feeding a pet). Alternately (or in addition, depending on the therapist's judgment), the participants might be assigned 6 tasks similar to ones carried out in the laboratory (3 easy and 3 more difficult) on a written check-off sheet to be performed repetitively with their more-affected arm. The tasks typically use materials that are commonly available (e.g., transferring dried beans on a spoon from one bowl to another) and are chosen for practice to improve the participant's most significant movement deficits. When responses to the MAL or check-off lists indicate a lack of performance, the therapist can then inquire into the reasons for this and problem-solve with the participant/caregiver on how to reverse this trend.

■ *Home skill assignments after treatment.*
Toward the end of treatment, a written individualized post-treatment home skill practice program is developed and given to the patient. There are 7 separate lists, one for each day of the week, which are to be repeated weekly. Each list contains 3 repetitive tasks to be carried out for 15–30 minutes and 7 ADL in which the participant is asked to use the more-affected hand selected from a list of approximately 400 developed by the laboratory.

■ *Post-treatment telephone contacts.*
Participants are contacted weekly for the month after treatment by telephone. During each contact the MAL is administered and problem solving is carried out.

■ *Function of the Transfer Package.*
In most rehabilitation regimens, the participant is required to carry out exercises guided by a therapist primarily during treatment sessions. The TP makes the patient a more active participant in their own improvement, not only during the treatment sessions but also at home. The TP provides a systematic means of specifying explicitly what the participant is expected to do when outside the treatment setting, monitoring what in fact is done, and providing a structure within which to solve apparent barriers to carrying out treatment goals. Thus, the TP permits participants to be immersed in a therapeutic environment for a meaningful portion of their day. Therapy is not confined to the limited period that the current system permits. It has been recognized by many therapists from the outset of the rehabilitation field that optimal therapy would be carried out 24 hours a day, 7 days a week ("24/7"). Application of the TP may represent an initial step in this direction.

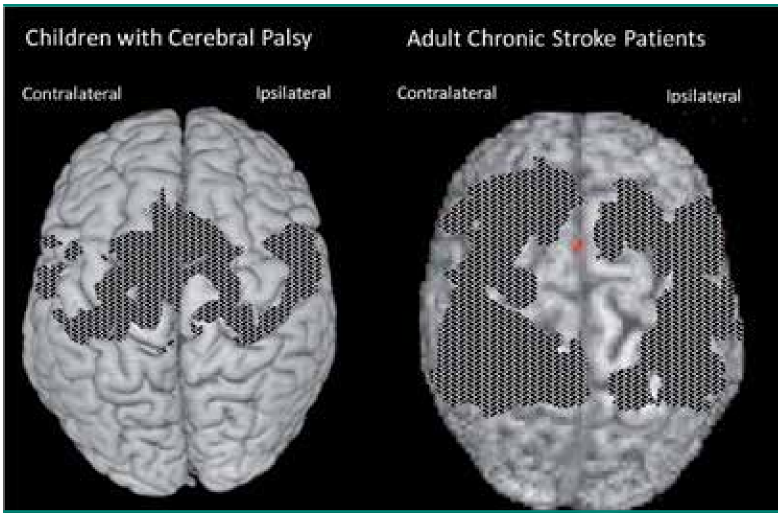

Fig. 1: Cortical surface-rendered image of grey matter change after CI therapy in a) children with hemiparetic cerebral palsy and b) adults with chronic stroke for comparison. Grey matter increases displayed on a standard brain. Surface rendering was performed with a depth of 20 mm. Cross-hatched areas indicate t statistics ranging from 2.0 to 6.7. Corrected for family-wise error.

Transfer Package Experiment

A 2 x 2 factorial experimental components analysis of CI therapy was carried out to assess the relative contribution made by the TP and shaping to the magnitude of the treatment effect [98]. Participants ($N = 40$) were outpatients ≥ 1-year post-stroke with mild/moderate hemiparesis (Grade 2). The different treatments, which in each case targeted the more-affected arm, lasted 3.5 hr/day for 10 weekdays. Two groups were given CI therapy with the TP, while two groups received the same treatment in the laboratory but were not given the TP. The second factor was shaping; two of the groups, one receiving the TP and one that did not, had their training administered by shaping and two groups received conventional task practice with no TP. Spontaneous use of the more-affected arm in daily life and maximum motor capacity of that arm in the laboratory were assessed with the Motor Activity Log (MAL) and the Wolf Motor Function Test (WMFT), respectively. Use of the TP, regardless of the type of training received, resulted in MAL gains that were 2.4 times as large as the gains in its absence ($P < 0.01$). The MAL gains were retained without loss one year post-treatment. An additional substudy ($N = 10$) showed that a single component of the TP, weekly telephone contact with participants for one month after treatment, doubled MAL scores at 6-month follow-up. Thus, the TP would appear to be a method for enhancing spontaneous use of a more-affected arm in the life situation. Immediately after treatment, voxel-based morphometry (VBM) analysis of MRI scores indicated that the two TP groups also exhibited a profuse increase in the amount of grey matter in the sensorimotor cortex, more anterior motor areas, and the hippocampus in both hemispheres (Fig. 1, right side) [24].

The groups not receiving the TP showed no change in amount of grey matter after treatment. Additional results from this experiment indicated that the TP substantially improved maximum motor capacity as indicated by performance made on request in the laboratory on the tasks of the Wolf Motor Function Test (WMFT). Shaping also improved maximal motor performance made on request in the WMFT, but it did not improve real world spontaneous use of the more-affected limb.

The question might arise as to whether the TP increases treatment effect by increasing the amount of practice of more-affected arm use. Alternatively, it is possible that the TP promotes integration of therapeutic gains achieved in the laboratory into real-world activities so that more-affected arm use becomes habitual. These two possibilities are not mutually exclusive. Addressing this question in future research would be of mechanistic and theoretical interest; however from the point of view of practical therapeutics, the resolution of this important issue does not really matter. The TP appears to be a means of increasing real-world treatment outcome that does not involve increasing costly therapist time; this would be of considerable value whatever the mechanism by which the TP achieved its effect.

CI Therapy in other Laboratories

At UAB, over 600 patients with stroke have been given one variant or another of CI therapy and all but 4 of these patients have demonstrated substantial improvement in motor ability (i. e., improvement greater than a Minimum Clinically Important Difference) [37, 42, 105, 111]. There have also been approximately 600 papers from other laboratories on adult and pediatric CI therapy published to date. To our knowledge all but two of the studies have reported positive results. In particular, CI therapy was the subject of a multi-site randomized controlled trial [119]; the results were strongly positive.

CI Therapy in Germany Compared to CI Therapy Elsewhere

With respect to magnitude of the treatment effect, this laboratory's results have been replicated with patients with chronic stroke in published studies from four laboratories where therapists were trained at UAB: the laboratories of Dettmers and Weiller [15], Miltner and Bauder [52], Flor and Kunkel [36], and Elbert and Sterr [75]; in the latter three studies, CI therapy was set up with the collaboration of the present author and then monitored twice yearly. In these studies some but not all elements of the TP were employed. However, in each case some TP elements were used and attention was focused on the transfer of therapeutic gains in the laboratory to spontaneous use of the more-affected arm in the life situation.

Some of the papers on CI therapy from elsewhere report outcomes as large as those obtained in this and the German laboratories just noted; however, most of these studies report results that are significant, but only one third to one half as large as those obtained here. The likely reasons for the reduced treatment effect in these laboratories are twofold: (1) there was incomplete or complete lack of use of the procedures of the transfer package, which, though reported in the papers from this laboratory, had been largely ignored. As noted above, we have replicated the reduced treatment effect obtained by others by duplicating everything that is normally done in treatment here except implementation of the TP [24, 98]. 2) A protocol with attenuated intensity (tasks or movements per unit time) was used, such as in a study by van der Lee et al. [112].

A comment should be made concerning the magnitude of the outcomes of the EXCITE multi-site randomized controlled trial of CI therapy. The treatment effects for the main variables were significant. However, while the amount of improvement on a laboratory motor function test where maximal motor performance was requested (Wolf Motor Function Test) was similar to that obtained at the UAB laboratory, the improvement in spontaneous use of the more-affected arm in the life situation was only one-half that typically obtained at UAB and the four German laboratories just noted. The reason for this reduced treatment effect may relate to the only partial implementation of the TP in the EXCITE trial. The behavior contract was employed, but six of the site PIs explicitly voted with one negative vote (by E.T.) not to monitor arm use in the life situation through daily administration of the MAL accompanied by problem solving to overcome apparent barriers to real-world arm use. Emphasis was not placed on transfer of treatment gains to real-world activities. Thus, the EXCITE trial, while successful, probably also represents significant evidence concerning the importance of the TP for achieving a maximal treatment effect.

Efficacy of CI Therapy in the Chronic Phase

The deafferented monkeys in the experiments in which the CI therapy rehabilitation techniques were developed were all in the chronic phase, more than 1 year after their surgical procedures. It therefore seemed that these techniques should work well with patients in the chronic phase if the translation of the CI therapy approach to humans was efficacious at all. However, the general, essentially axiomatic belief in the rehabilitation field at the time was that the impaired movement of a stroke victim could not be modified in the chronic phase no matter what technique was employed. This view still has considerable force. Even today, after 25 years of research and clinical practice, many of the chronic patients who come to UAB for CI therapy have been told by their physicians and therapists that there is nothing that can be done to improve their motor deficit. Five years ago, this was true for as many as half of the patients treated.

CI Therapy: Constraint vs. Restraint

The movement-restriction and training situations of CI therapy share a common feature. They both are powerful means of inducing use of the more-affected arm. One procedure physically restrains the less-affected arm so that the individual must use the more-affected extremity to avoid being rendered more dependent or, in the case of the unilaterally deafferented monkeys, virtually helpless. The other method, training, induces use of the more-affected arm by structuring a situation so that the limb must be used in order to achieve success or avoid failure. Thus, both procedures constitute constraints that promote use of the more-affected arm by a major alteration of environmental conditions. Though the name is accurate, the use of the term »constraint« in the title of the therapy has turned out to be confusing. The most salient aspect of CI therapy to a casual observer is that the less-affected arm is *restrained*. Moreover, the rehabilitation field was not used to thinking of training as imposing a constraint on behavior. Instead, the large majority of professionals interpreted the focal word in the name of the therapy as being an alternate way of saying “restraint”. Thus, the general impression arose that restraint of the less-affected arm was the central and most important feature of the therapy. As indicated below, that is very far from being true; physical restraint of the less-affected arm can be dispersed with entirely in achieving a maximal result if the training conditions are arranged appropriately. Recently, the field has begun to accept that the word “constraint” is meant to include training, but that understanding is still only partial.

As noted, variants of the CI therapy that do not involve physical restraint of the less affected arm have been found to be as efficacious as the initial protocol [85, 93, 95, 107]. These include (1) placement of a nonrestrictive half-glove (with fingers cut off) on the less-affected arm as a reminder not to use it and shaping of the paretic arm, and (2) shaping of the paretic arm only [107]. The half-glove intervention was designed so that CI therapy could be employed with patients who have balance problems and might be at risk for falls when wearing a sling; this intervention expanded the population of stroke patients amenable to CI therapy threefold. Currently, a padded or protective safety mitt is used instead of the half glove. This restraint leaves the less-affected arm free so as not to compromise safety, but prevents use of the hand and fingers in activities of daily living (ADL).

Thus, there is nothing talismanic about use of a restraint device. Any rehabilitation technique that requires that the more-affected arm be used extensively should be efficacious. Recently a type of rehabilitation termed »bilateral training« has been reported to yield good clinical results. In the defining exercise patients are required to use the two arms, both the more-affected and less-affected, to accomplish a task. Bilateral training is sometimes contrasted to CI therapy where the focus of therapeutic attention is on inducing patients to use a more-affected arm more extensively. However, the contrast is superficial, based just on the nature of the training exercises employed. Both techniques require that the more-affected arm be used more extensively than before treatment, for unilateral tasks in CI therapy and in bilateral tasks in bilateral training. Use of bilateral tasks has a forcing function with respect to use of the more-affected arm, the same therapeutic objective as CI therapy. Which type of training exercise is more efficacious is an empirical question. It should also be noted that the two types of training exercises are not mutually exclusive. For example, in the pediatric variant of upper extremity CI therapy (PCIMT) treatment for hemiplegic cerebral palsy is carried out for 15 consecutive days. For the first 13 days the less-affected arm is casted, but on the last two days the cast is removed and training is carried out in bilateral activities [89]. Bilateral training has also been carried out during rehabilitation in other laboratories [summarized in 26] with success.

Severity of Deficit, Chronicity, and Lower Extremity CI Therapy

Lower Functioning Patients

Most of the patients treated at UAB could be characterized as having deficits that were mild/moderate, defined primarily as having the ability to extend 20° at the wrist and 10° at each of the fingers (Grade 2; see Table 1 for full active range of motion criteria). Experiments have also been carried out with patients with moderate and moderately severe deficits (Grades 3 and 4) [100]. Their treatment change was somewhat less than for higher functioning patients, e.g., increases of approximately 400% and 350% for patients with moderate and moderately severe deficits, respectively, compared to approximately 500% for patients with mild/moderate deficits, but the treatment changes were nevertheless very large. Most recently, work has been carried out with patients with useless, plegic hands that were initially fisted [96, 106]. Conventional physical rehabilitation procedures, including some from neurodevelopmental treatment (NDT), and functional electrical stimulation (FES) were used to maintain the fingers in a sufficiently extended and aligned position so that CI therapy training procedures could be carried out. At the end of treatment, the patients exhibited a 186% improvement in the real-world use of the more-affected arm. It had been converted into a useful "helper" in the life situation (e.g., keeping a piece of paper in place while writing with the less-affected hand, holding a toothpaste tube while unscrewing the cap, bearing body weight for bed mobility).

We estimate that CI therapy is applicable to at least 50% of the chronic stroke population with motor deficit, perhaps more. CI therapy would also be appropriate for a sizable percentage of individuals who had traumatic brain injury in previous years.

Chronicity

A large majority of previous CI therapy studies were with chronic and subacute patients with stroke. Several studies with acute patients beginning CI therapy 7–14 days post-event reported little [5, 19] or no [18] treatment effect. However, a number of other studies have obtained results as good as those obtained with chronic and subacute patients [57]. The reasons for the weak early results may be related to the interference in American hospitals of the ward routine with adequate administration of CI therapy. In any case, the preponderance of evidence now is that CI therapy is efficacious in the acute phase.

Lower Extremity

CI therapy techniques were developed for the rehabilitation of the upper extremity. An obvious target for transfer of this approach was to the more-affected lower extremity of stroke patients. The 38 patients with chronic stroke treated in controlled experiments to date have had a wide range of disability extending from being close to non-ambulatory to having moderately impaired coordination [100]. The treatment (Lower Extremity-CI therapy or LE-CI therapy) consists of massed or repetitive practice of lower extremity tasks (e.g., over-ground walking, treadmill walking with and without a partial body weight support harness, sit-to-stand, lie-to-sit, stair climbing, walking over obstacles, various balance and support exercises) for first six, now three hours/day with interspersed rest intervals as needed over three weeks with an additional 0.5 hours/day devoted to TP procedures. Task performance is shaped as in the upper extremity protocol. Training is enhanced through the use of force feedback (limb load monitor) and limb displacement (joint angle/electric goniometer) feedback devices. No restraining device is placed on the less-affected leg. The lower-extremity procedure is considered to be a form of CI therapy because of the use of the TP, the strong massed practice/shaping element, and because the reward of adaptive patterns of ambulation over maladaptive patterns in our training procedure constitutes a significant general form of constraint. Control data were provided by a general fitness control group that received the same battery of lower-extremity tests as the treatment subjects. The Effect Size of the change in real-world performance due to the treatment was large, but not quite as large as for the upper extremity. The improved lower extremity use was retained without any decrement for the two years that were tested. On a non-experimental basis, lower extremity CI therapy has been administered clinically at UAB for the past 10 years.

Conditions other than Stroke

The CI therapy protocol has been applied with success to traumatic brain injury [71], upper and lower extremity in multiple sclerosis [46, 47], cerebral palsy and pediatric motor disorders of neurological origin across the full range of age from one year old through the teenage years [88, 89, 94], focal hand dystonia in musicians [8, 9], and the increased use element of CI therapy has been effective for phantom limb pain after amputation [114].

Aphasia

In a substantial number of stroke patients, because of halting and slow verbal production and incomplete understanding, speech becomes very effortful and often embarrassing. The person compensates by greatly reducing attempts to speak or remaining silent entirely and by using gestures and other nonverbal means of communication. The demonstration that motor deficits are modifiable in chronic stroke raised the possibility that verbal impairment could also be rehabilitated by an appropriate modification of the CI therapy protocol. The LNU formulation predicted that this was a strong possibility. In the initial study, by Pulvermüller, Taub, and coworkers [64, 76], aphasic patients with chronic stroke who had previously received extensive conventional speech therapy and had reached an apparent maximum in recovery of language function were induced to talk and improve their verbal skills by engaging them in a language card game for three hours each weekday over a two-week period. The intervention was termed Constraint-Induced Aphasia therapy (CIAT I). Constraint was imposed by the contingencies of reinforcement in the shaping paradigm that was used; there was no physical restraint, though as noted, physical restraint is not necessary to obtain a good result with CI Movement therapy. Groups of three patients and a therapist participated in the language card game [63, 65]. The exercise resembles the child's card game "Go Fish". A participant asks one of the other players if they have in their hand a card with a specific pictured object to match one in their own. If they do, the requester can meld those cards. Participants win the game if they meld each of the cards they were dealt so that none are left. The difficulty of the required request by each patient is progressively increased in small steps (i. e. shaped) along several dimensions: number of words in the request (or response to it), number of formulas of politeness, precision of patient's card description (animal/pet/dog), complexity of objects depicted on a card (dog/2 dogs/1 red and 1 blue dog), and grammatical correctness.

The original Pulvermüller protocol, developed 10 years before the CIAT I intervention, produced a positive treatment outcome, but it was modest. The addition of shaping led to a substantially increased effect. The study participants improved much more than patients receiving conventional aphasia therapy. This study has since been replicated (e. g. [4, 30, 44, 50, 51]). Following a positive evaluation of a committee appointed by the American Speech and Hearing Association [66], CIAT I is now beginning to spread. The results of the CIAT I protocol have been positive; however, the intervention was only an incomplete translation of CI Movement therapy. CIMT produces an improvement of approximately 500 % in real-world use of the more-affected extremity of chronic stroke patients with mild to moderate motor deficit in the UAB laboratory [97]. Aphasic patients given CIAT I showed an improvement of 30 % in real-world verbal behavior. This is a large treatment effect compared to conventional speech language therapies, but it is very small compared to the results produced by CIMT. Consequently, in order to determine whether the large difference was the result of an incomplete translation of the CI therapy protocol employed in the UAB laboratory with motor deficits to the treatment of language impairment, the initial aphasia treatment protocol (CIAT I) was modified to more closely resemble the CIMT protocol.

In the restructured and enhanced protocol (CIAT II) [29], revisions involved addition of new exercises, including a final exercise, considered to be the most important, in which everyday verbal interactions were simulated and modeled. In addition a transfer package parallel to that used in CIMT was introduced, there was increased emphasis on the shaping of responses, and the primary caregiver was trained as an alternate therapist with their training beginning in the laboratory but focused largely on the at-home practice of verbal behavior. To date, only 4 patients have been treated with the new protocol. However, their results have far exceeded those obtained with CIAT I and are comparable to the results obtained with CIMT. With CIAT I, as noted, there was a 30 % improvement in real-world verbal behavior; for the recent patients, the mean improvement was approximately 200 %. Of additional interest is the fact that in the six months following the completion of treatment verbal behavior scores increased substantially. This increase would appear to be attributable to the continuation of training by the caregivers in the real-world environment.

Mechanisms Responsible for CI Therapy Treatment Effect

Evidence suggests that there are at least two mechanisms that underlie the treatment effect of CI therapy: 1. Overcoming learned nonuse, 2. Use-dependent plastic brain reorganization.

Learned Nonuse

The learned nonuse mechanism was proposed in the context of the primate somatosensory deafferentation studies referred to at the beginning of this article [79, 80]. It was formulated as a means of resolving a central enigma posed by the Mott and Sherrington experiment of 1895 [56]. Why did monkeys not use a single deafferented limb? Sherrington's reasonable answer had been that extremity deafferentation interrupted the afferent limb of spinal reflexes, and it was this that abolished use of the extremity even though motor innervation remained intact. Hence the idea emerged that spinal reflexes were the basic building blocks from which behavior was elaborated, which was the fundamental tenet of Sherringtonian reflexology. This was a pervasive view in neurology for the first 70 years of the 20th century. However, the two simple behavioral techniques noted above enabled very extensive and purposive use of a deafferented limb from which all myotatic reflex activated had been abolished. This demonstration and later control experiments showed that the Sherringtonian reflexological explanation of the primate unilateral deafferentation experiments in this formulation could not be correct. What then could account for the absence of purposive movement after unilateral forelimb deafferentation? The need to address that salient question led to the formulation of the concept of learned nonuse.

Several converging lines of evidence suggested that nonuse of a single deafferented forelimb is a learning phenomenon involving a conditioned suppression of movement termed learned nonuse (LNU). The restraint and training techniques appear to be effective because they overcome learned nonuse. We offer the following explanation for further empirical test and hypothesis formation, though several central predications stemming from this formulation have been experimentally verified [79, 80].

Substantial neurological injury usually leads to a depression in motor and/or perceptual function that is considerably worse than the level of function that will be attained after spontaneous recovery has taken place. The processes responsible for the initial depression of function and the later gradual recovery that occurs at the level of both the spinal cord and the brain is, at present, incompletely understood. Whatever the mechanism, however, recovery processes come into operation following deafferentation so that after a period of time movements can once again, at least potentially, be expressed. In monkeys the initial period of depressed function lasts from 2 to 6 months following forelimb deafferentation [79, 80].

Thus, immediately after surgical deafferentation of a forelimb, monkeys cannot use that extremity; recovery from the initial depression of function requires considerable time. Animals with one deafferented forelimb are unsuccessful in attempts to use that extremity during this period. Efforts to use the deafferented limb often lead to painful and otherwise aversive consequences, such as incoordination and falling, loss of food objects, and in general, failure of any activity attempted with the deafferented limb. Many learning experiments have demonstrated that punishment has the effect of suppressing the behavior associated with it [1, 10, 23]. The monkeys, meanwhile, get along quite well in the laboratory environment on three limbs and are therefore positively reinforced for this pattern of behavior which, as a result, is strengthened. Thus, the response tendency to not use the affected limb persists and, consequently, monkeys never learn that the limb has become potentially useful several months after surgery.

When the movements of the intact limb are restricted several months after unilateral deafferentation, the situation is changed dramatically. Animals either use the deafferented limb, or cannot with any degree of efficiency feed themselves, locomote, or carry out large portions of their daily activities. This new constraint on behavior increases the drive to use the deafferented limb, thereby inducing monkeys to use it and overcoming the learned nonuse. However, current ongoing environmental contingencies, such as the relative inefficiency of the affected upper extremity compared with the unaffected arm, continue to strengthen use of the affected extremity. However, if a movement-restriction device is placed on the intact forelimb and left on for several days or longer, use of the deafferented limb acquires strength and then when the device is removed can compete successfully with the strongly over-learned nonuse of that limb.

The conditioned response and shaping conditions described above, just like the restriction of the intact limb, place major constraints on the animals' behavior. In conditioned response situations, if the monkeys do not perform the required response with the deafferented limb, they are either punished or do not receive food pellets or liquid when hungry or thirsty, respectively. Similarly, during shaping, reward is contingent on making an improved movement with the deafferented limb. The monkeys cannot get by using just the intact forelimb as they can in the colony environment. These new sets of conditions, just as the movement-restriction device, constrain the animals to use their deafferented limb to avoid punishment or obtain reward and thereby induce the animals to use their deafferented limb and overcome the learned nonuse.

Learned Nonuse Formulation as the Origin of CI Therapy and its Multiple Applications

The concept of learned nonuse was developed in the context of primate deafferentation experiments. It was proposed as an alternate to the reflexological explanation of the results of unilateral forelimb deafferentation, which our early experiments showed could not be correct. However, the formulation of LNU was not specific to somatosensory deafferentation. The central tenet was based on the regional loss of neuronal excitability observed to follow any substantial damage to the central nervous system (CNS). Thus, if the LNU formulation was correct, as the experimental tests of two counterintuitive predications [79, 80, 99] seemed to indicate, then it ought to apply to other types of CNS damage. This line of reasoning led directly to the attempt to improve motor deficit after stroke in humans by the same two techniques that had been employed with unilaterally deafferented monkeys: intensive training of the more-affected arm and restraint of the less-affected arm.

The applicability of LNU to humans after stroke was considered reasonable [80], but initially we were not completely confident that it was correct. There was the interspecies difference, and the fact that the initial tests of the LNU formulation were with respect to somatosensory deafferentation and not with any other type of CNS lesion. However, once the LNU formulation and the techniques used to overcome LNU after deafferentation in monkeys were shown to be applicable to humans after stroke [90], the extension of these techniques to motor deficits resulting from other types of damage to the CNS in humans was straightforward. These have included to date, as noted above, traumatic brain injury, cerebral palsy and other types of injury to the immature nervous system, multiple sclerosis, and spinal cord injury. Extension of the basic CI therapy protocol from the upper extremity to the lower extremity was equally straightforward. All of these applications of the CI therapy protocol involved remediation of motor deficits. Thus, some question arose concerning whether the principles of CI therapy would be applicable to post-stroke aphasia. LNU has been demonstrated to occur in post-stroke aphasia [13] and it is a phenomenon generally recognized to be common by many speech-language pathologists. However, while speech clearly consists of a series of motor acts, it diverges from movements of the extremities in that it is intimately associated with comprehension and the elaboration of linguistic structures that have no obvious counterparts in extremity movement. Now that the principles of CI therapy have been successfully applied to post-stroke aphasia, its relevance seems straightforward. However, it was not clear that this would be the case at the outset.

A final point to be made is that the use of the CI therapy protocol to improve the motor deficit after stroke stems primarily from the LNU formulation, as does each of its subsequent applications to other pathological conditions. The fact that these predicted applications have been successful constitutes an additional source of evidence in support of the LNU formulation.

Use-Dependent Brain Reorganization

In a seminal series of studies Merzenich and co-workers showed that increased use of a limb and the resulting increase in afferent inflow leads to an expansion of the cortical representation zone of that body part in new-world monkeys [28, 67–69]. Elbert, Taub, and co-workers [6, 20, 21] reported that the same phenomenon occurs in humans. It was next found that CI therapy-type interventions involving training of extremity use after a CNS injury results in both improved extremity function and reorganization of brain activity. Nudo and co-workers demonstrated this first in new world monkeys [58] showing that the area surrounding a motor cortex infarct that would not normally be involved in control of the hand came to participate in that function at the same time that performance on an experimental task involving manual dexterity improved. In humans whose upper extremity function had been enhanced by CI therapy, Liepert et al. [40, 41] used focal transcranial magnetic stimulation to show that the cortical representation of an important muscle of the hand (abductor pollicis brevis) was greatly enlarged. CI therapy had led to an increase in the excitability and recruitment of a large number of neurons in the innervation of movements of the more-affected limb adjacent to those originally involved in control of that extremity prior to treatment. At about the same time, Kopp et al. [35], using EEG source imaging, found that after CI therapy the motor cortex ipsilateral to the more-affected arm, which normally controls movements of the less-affected arm, had been recruited to generate movements of the more-affected arm. The finding that CI therapy is associated with substantial changes in brain activity was confirmed in other early studies in which the author collaborated involving the "Bereitschaftspotential" [3] and positron emission tomography [116]. To date, there have been more than 20 studies, many involving functional magnetic resonance imaging, that have obtained similar results (summarized until 2006 by Mark, Taub, and Morris [48]).

The studies just described employed functional brain imaging and brain mapping techniques to demonstrate that CI therapy could alter the function of specific brain regions. The question remained whether CI therapy could measurably alter brain structure in humans. Starting at the beginning of the first decade of this century it was shown that experienced taxi drivers have significantly expanded hippocampi [43], jugglers acquire significantly increased temporal lobe density [16], and thalamic density significantly declines after limb amputation [17]. Moreover, in an animal model of stroke, CI therapy combined with exercise reduced tissue loss associated with stroke [14]. Accordingly, structural imaging studies became a logical initial step toward understanding whether there are anatomical changes following the administration of CI therapy and whether these are correlated with clinical improvements.

Longitudinal voxel-based morphometry (pre- vs. post-treatment) was performed on subjects enrolled in our study of the contribution made by the TP to CI therapy outcome [24]. It was found that structural brain changes paralleled changes in amount of use of the impaired extremity for activities of daily living. Groups receiving the TP showed profuse increases in grey matter tissue in sensorimotor cortices both contralateral and ipsilateral to the more-affected arm, as well as in bilateral hippocampi. The aforementioned sensorimotor clusters were bilaterally symmetrical and encompassed the hand/arm regions of primary sensory and motor cortices as well as the supplementary motor area and portions of Brodmann's area 6 (Fig. 1, right side). It was of importance that increases in grey matter were significantly correlated with increases on the MAL for the sensorimotor clusters on both sides of the brain and the predefined hippocampus region of interest (r's $>.45$). Thus, this change in the brain's morphology is directly related to administration of the TP which in turn substantially increases the amount of real-world use of the affected arm. In contrast, the groups that did not receive the TP showed relatively small improvements in real-world arm use and failed to demonstrate grey matter increases. In addition, the increase in grey matter from pre-to post-treatment differed significantly between groups. The fact that the anatomical change is directly related to the TP lends increased credibility to the importance of the TP.

In another study [74], children with hemiparetic cerebral palsy also showed increases in grey matter in the bilateral sensorimotor cortices (Fig. 1, left side). These changes showed a strong correlation with improvements in spontaneous real-world arm use as recorded on the pediatric version of the MAL. More focal increases occur in children. This finding is consistent with previous research, which has shown that, compared to children, adults show significantly more widespread cortical activation when a manual task is performed including not only bilateral sensorimotor cortices as in children but parietal and supplementary motor areas as well [45].

It is not possible to make a causal attribution regarding the observed cortical structural changes and improvement in motor function. The grey matter increase could be either a cause or an effect of increased motor ability and behavioral change, or it could simply be an independent accompaniment. However, the trend observed for a correlation between increases in grey matter volume and magnitude of motor improvement raises the possibility of a causal relationship. Future research with either animals or humans in which CI therapy is administered and cortical structural change is suppressed may resolve this issue.

In both studies increases were also observed in the grey matter of the hippocampus, which may have included the adjacent subventricular zone. The hippocampus is known to be involved in learning and memory and these two processes are associated with the improved limb use that occurs with CI therapy. Evidence also indicates that stem cells are located at this site in the adult mammalian brain [22, 120] and simulated stroke in animals can increase the quantity of these cells [120]. One might speculate that the increases in grey matter observed in the hippocampal region and sensory and motor areas of the brain are mediated in part by increased production of neuronal or glial stem cells that might participate in the migratory repair of an infracted area [33]. Alternatively, or in addition, grey matter increases may result from rehabilitation – induced increases in dendritic arborization and synaptic density [7], and possibly gliosis or angiogenesis. Determination of which of these processes or combination of processes responsible for the observed increase in grey matter following CI therapy awaits future research.

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Conflict of interest

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