

CONSTRAINT-INDUCED MOVEMENT THERAPY: BRIDGING FROM THE PRIMATE LABORATORY TO THE STROKE REHABILITATION LABORATORY

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In this laboratory we have developed a set of techniques that randomized controlled studies indicate can substantially reduce the motor deficit of patients with mild to moderately severe chronic strokes. The techniques, termed Constraint-Induced Movement therapy (CI therapy), involve motor restriction of the less-affected arm while at the same time intensively training the more-affected arm. The intervention was derived directly from basic research with monkeys. The primary difference between CI therapy and conventional physical therapy is in the duration and intensity of the treatment. The greatly improved extremity function produced in the laboratory transfers to the activities of daily living outside the clinic. Treatment gains persisted for the two years tested. Converging data from seven experiments has shown that CI therapy produces massive alterations in brain organization and function correlated with the large improvements in motor ability that it produces.

Key words: rehabilitation, physical therapy, cortical reorganization, learned nonuse, stroke, neurological injury

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INTRODUCTION

Stroke is a highly prevalent condition that results in very high costs to the individual and society. In this laboratory we have developed a technique for substantially reducing the incapacitating motor deficit of the upper extremity in many stroke patients and greatly increasing use of the more-impaired extremity in the life setting (1–4). The technique is termed Constraint-Induced Movement therapy (CI therapy) and it has been demonstrated to be effective in multiple studies using between- and within-subject controls as well as convergent measures from multiple domains. In addition, it has been shown to produce a large transfer of increased limb use to the activities of daily living in the home situation. It involves training of the more-affected extremity for many hours daily for a period of consecutive weeks (i.e. massing of practice or repetitive training) and, less importantly, restrain-

ing the less-affected hand in a protective safety mitt or the entire arm in a sling for a target of 90% of waking hours during the treatment period. Using one portion or the other of the full treatment regimen (5–9), or both components (10–14), or an attenuated version of the procedure (15–20), investigators in other laboratories have also obtained positive results with patients after stroke. An authoritative literature review (21) stemming from an NIH consensus conference cites CI therapy as being only one of three treatments for which there is evidence of clinical efficacy and the only one to: 1) be supported with evidence from controlled randomized studies, and 2) have been shown to be effective for the upper extremity. Moreover, the proposed intervention does not involve medications or side effects, and there are no significant risks.

EXPERIMENTS WITH NON-HUMAN PRIMATES

CI therapy is derived from basic behavioral neuroscience research with primates conducted by Taub and coworkers. When a single forelimb is surgically deafferented in a monkey, the animal does not make use of it in the free situation (22–24). However, the monkey can be induced to use the deafferented extremity by restricting movement of the intact limb (25, 26). If movement restriction is imposed for only one 24-hour period, the animal will use the limb while in the restriction device but will revert to non-use of the extremity as soon as the device is removed. However, if the restriction device is allowed to remain in place for a longer period, for example one week of 24-hour per day restraint, the ability to use the affected extremity transfers from the movement restriction condition to the life situation and becomes permanent. A useless limb is thereby converted into a limb capable of extensive movement (1). Conditioned response and shaping techniques are another behavioral means of overcoming the inability to use a single deafferented limb in primates (summarized in 1, 27).

During this the last century, several investigators have found that a behavioral technique could be employed in animals to substantially improve a motor deficit resulting from neurological damage (28–31). However, none of these observations were embedded in a formal theoretical context that permitted prediction nor was the generality of the mechanism clearly recognized. Consequently, these findings remained a set of disconnected observations that received little attention. Moreover, no systematic attempt was made to apply this approach to humans.

A POSSIBLE MECHANISM

Several converging lines of evidence suggested that nonuse of a single deafferented limb is a learning phenomenon involving a conditioned suppression of movement. (For a description of the experimental analysis leading to this conclusion, see 1, 27). As a background for this explanation, one should note that substantial neurological injury usually leads to a depression in motor and/or perceptual function that is considerably greater than will eventually be possible after spontaneous recovery of function has taken place. The process responsible for the initial depression of function and the later gradual recovery of function, which occurs at the level of both the spinal cord and the brain, is at present incompletely understood. However, regardless of the mechanism, 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 2–6 months following forelimb deafferentation (27).

Thus, monkeys that have sensation surgically abolished from a forelimb cannot use their deafferented limb for some months after the operation; recovery of the motor neurons from the initial depression of function induced by the surgical insult requires considerable time. An animal with one deafferented limb tries to use that extremity in the immediate postoperative situation but it cannot accomplish coordinated movements. However, it gets along quite well in the laboratory environment on three limbs and is therefore positively reinforced for this pattern of behavior, which, as a result, is strengthened. Moreover, continued attempts to use the deafferented limb often lead to painful and otherwise aversive consequences, such as incoordination and falling, as well as to loss of food objects, and, in general, failure of any activity attempted with the deafferented limb. These aversive consequences condition the animal to stop using their deafferented limb. (Many learning experiments have demonstrated that punishment results in the suppression of behavior (32).) This response tendency persists, and consequently the monkeys never learn that several months after operation, after the depression of function of the motor neurons lifts, the limb has become potentially useful. In addition, following stroke in humans (33, 34) and presumably after extremity deafferentation, there is marked contraction in the size of the cortical representation of the limb; this is probably correlative with the report of patients with stroke that movement of that extremity is effortful. These three processes (i.e. punishment of use of the deafferented limb, reinforcement of use of the intact limb, and cortical reorganization) interact to produce a vicious spiral downward that results in a learned nonuse of the affected extremity that is normally permanent.

When the movements of the intact limb are restricted several months after unilateral deafferentation, the situation is changed dramatically. The animal must use the deafferented limb to function with any degree of efficiency. This change in motivation overcomes the learned nonuse of the deafferented limb. The conditioned response and shaping conditions noted above, just like

the restriction of the intact limb, also involve major alterations in motivation. For a fuller account of these alterations, see (1).

A similar analysis could also be relevant to human patients after brain injury or stroke (1). The period of temporary, organically based inability to use a more-affected upper extremity would be due to cortical mechanisms rather than processes associated with deafferentation at the level of the spinal cord. With respect to humans, the model does not incorporate some modifiers, such as co-morbidities or psychosocial support that could potentially influence the mechanisms underlying learned nonuse and those to overcome it. Moreover, the learned nonuse model does not in any way minimize the obvious general correlation between amount of neural damage following CVA (especially at the level of the medullary pyramids) and the amount of motor function that is recovered on the more-affected side. Such a correlation could be a sufficient explanation for the observed differences in amount of recovery among many patients. However, the fact that some patients with a given extent and locus of lesion recover more movement than other patients with stroke having similar lesions suggests that additional factors may be involved. One of these factors might be the operation of a learned nonuse mechanism. Support for this view comes from the fact that a measure of learned nonuse developed in this laboratory by Mark & Taub (i.e. a measure of ability to use a more-affected extremity when asked to do so in the laboratory minus a measure of actual amount of use of that extremity in the life situation) correlates $r = 0.49$ ($p < 0.0001$), with CI therapy treatment outcome, while the component measures of this index correlate either not at all (initial laboratory motor function) or significantly but weakly (initial life situation use) with treatment outcome. The strength of the correlation of treatment outcome with a presumed measure of learned nonuse suggests that this measure is an index of a real entity. An additional type of evidence has been obtained in another study (35).

USE-DEPENDENT CORTICAL REORGANIZATION: A LINKED BUT INDEPENDENT MECHANISM

An intracortical microstimulation (ICMS) study with monkeys and 7 studies with humans making use of focal transcranial magnetic stimulation (TMS), neuroelectric source imaging, PET, analysis of the readiness potential, and functional magnetic resonance imaging (fMRI) carried out by 5 groups of investigators, suggest that cortical reorganization may be associated with the therapeutic effect of CI therapy. Following the seminal work of Jenkins et al. on use-dependent cortical reorganization in monkeys (36–38) imaging studies showed that the same phenomenon occurs in humans. For example, Elbert et al. (39) found that the cortical somatosensory representation of the digits of the left hand was larger in string players, who use their left hand for the dexterity-demanding task of fingering the strings, than in nonmusician

controls. Moreover, the representation of the fingers of blind Braille readers, who use several fingers simultaneously to read, was enlarged (40). These results, in conjunction with research on cortical reorganization in adult monkeys (41) and human phantom limb patients (42), suggest that the size of the cortical representation of a body part in adult humans depends on the amount of use of that part. The ICMS studies by Nudo et al. (43) demonstrated in adult squirrel monkeys that were surgically given an ischemic infarct in the cortical area controlling the movements of a hand, that training of the more-affected limb resulted in a cortical reorganization. Specifically the area surrounding the infarct not normally involved in control of the hand came to participate in that function. These findings suggest the possibility that the increase in more-affected arm use produced by CI therapy results in a use-dependent increase in the cortical representation of the more-affected arm, which provides the neural basis for a permanent increase in the use of that extremity. This hypothesis has been confirmed in TMS studies which showed that the cortical region from which EMG responses of a hand muscle can be elicited by TMS were almost doubled after CI therapy in chronic stroke patients compared to the pretreatment period (33, 44). This experimental evidence that CI therapy is associated with a use-dependent increase in cortical reorganization has been further confirmed by convergent data from three other laboratories with which Taub collaborates (13, 44, 45) and by an fMRI study (12). These recent studies represent a demonstration of an alteration in brain organization or function associated with a therapy-induced improvement in the rehabilitation of movement after neurological injury in humans.

EXPERIMENTS WITH HUMANS AFTER STROKE

Bach-y-Rita et al. (46, 47) and Franz et al. (48), not operating within a CI therapy context, used training techniques based on physical therapy procedures to obtain improvements in upper extremity use in chronic stroke patients whose greatly impaired motor function was presumably not amenable to further recovery. Bach-y-Rita's discussion of the possibility that the motor function of chronic stroke patients is modifiable is particularly significant. In addition, Balliet et al. (49), Wolf et al. (50, 51) and Basmajian et al. (52, 53) among others have used training techniques based on EMG biofeedback to improve motor ability in chronic stroke patients. The initial work with patients with stroke that made explicit use of part of the CI therapy approach was carried out by first Ince (6) and then Halberstam et al. (5), who used one of the simple conditioned response paradigms developed in the deafferentation research noted above in successful attempts to improve motor capacity following stroke. For some time this work was not followed up.

Subsequent to the research showing that in unilaterally deafferented monkeys both motor restriction of the unaffected upper extremity and training of the affected extremity can overcome long-standing nonuse of the more-affected limb, an article

was published suggesting that the same two techniques could be transferred to humans and might be of value for improving chronic motor deficits after stroke (1). Wolf and co-workers employed one of the two suggested techniques, restriction of the less-affected extremity, to induce a reliable remediation of motor impairment in chronic stroke patients (7, 9). To determine if adding a variant of the second component of the suggested protocol (i.e. simple practice of use of the more-affected extremity but not explicit training as had been carried out in the animal work), would increase the motor improvement noted by Wolf and co-workers, a pilot experiment was carried out by Taub and co-workers (2).

Subjects in this study were patients with chronic stroke who had experienced CVAs from one to eighteen years earlier (mean chronicity = 4.4 yrs). Patients with this degree of chronicity had traditionally been presumed to have reached a plateau in their motor recovery and were not expected to exhibit any further improvement. Nine persons who met the initial study's inclusion criteria, including possession of 20° active extension at the more-impaired wrist and 10° active extension at each of the more-impaired finger joints (51), were assigned by a random process either to an experimental group (n=4) or an attention-placebo control group (n=5). Patients in the experimental group signed a behavioral contract in which they agreed to wear a sling on their less-affected arm for a target of 90% of waking hours for 14 days. On 10 of those days, they received 6h of supervised task practice using their more-affected arm on a variety of ADL tasks interspersed with 1 h of rest. Treatment efficacy was evaluated using the Wolf Motor Function Test (WMFT) (9, 54), the Arm Motor Ability Test (AMAT) (2, 55, 56), and the Motor Activity Log (MAL) (2, 57) which tracks arm use in a number of ADLs through a semi-structured interview administered independently to patients and caregivers. The experimental group demonstrated a significant increase in motor ability as measured by both laboratory motor tests (WMFT, AMAT) over the treatment period, whereas the control patients showed no change. The improvement on the WMFT was, depending on the measure used, three to four times as great as in the work of Wolf et al. (7, 9). This presumably reflects the effect of expanding the protocol by adding practiced, repetitive movements to motor restriction of the unaffected limb; indeed, subjects given intensive training only and no restraint exhibit 80% of the full treatment effect post-treatment. On the MAL, the experimental group showed a very large increase in real-world arm use over the two-week period and demonstrated no decrement in the gains over a two year follow-up period. The control patients exhibited no change or a decline in arm use over the same period.

PLACEBO-CONTROLLED TRIAL

These results have since been confirmed in an experiment from this laboratory (58, 59) using less-affected arm constraint and training (by shaping) of the affected arm instead of task practice, with a larger sample (20 subjects) and a credible placebo control

group of equal size. The placebo control group was designed to better control for the duration and intensity of the therapist-patient interaction and the duration and intensity of therapeutic activities than in the previous study. The placebo control subjects were given a general fitness program in which they performed strength, balance, and stamina training exercises, played games that stimulated cognitive activity, and practiced relaxation skills for the same number of hours/day (6) as the CI therapy subjects for 10 days. As in other experiments, the treatment group demonstrated a significant increase in motor ability as measured by the WMFT and a very large increase in real-world arm use over the intervention period. The control subjects displayed a small but significant improvement at the end of treatment, but by 3 months after treatment this effect had disappeared. (It should be noted that a small but transient positive effect is what might be expected from an adequate placebo control procedure). There was a significant difference in the change score between groups from pre- to post-treatment ($p < 0.0001$) and also at the 3-month follow-up point ($p < 0.0001$). The 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 (60), suggested that they found the control intervention to be credible. These studies from our laboratory have been replicated in published studies from 3 other laboratories (34, 61–63). In addition, a number of other researchers have evaluated the sling plus shaping intervention or components of it with positive results (8, 10–14, 17–19, 64).

ADDITIONAL CI THERAPY EXPERIMENTS WITH HUMANS AFTER STROKE

These experiments indicate that there is a family of techniques that can overcome learned nonuse (4, 65). The other interventions that have been tested are: 1) placement of a half-glove on the less-affected arm as a reminder not to use it and shaping of the paretic arm, 2) shaping of the paretic arm only, 3) intensive physical therapy (aquatic therapy, neurophysiological facilitation, and task practice) of the paretic arm for 5 h/day for 10 consecutive weekdays. 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 expands the population of stroke patients amenable to CI therapy threefold. More recently, a protective safety mitt has been used; it leaves the less-affected arm free so as not to compromise safety, but prevents use of the hand and fingers in ADL. All these groups showed increases in real-world arm use over the treatment period that were equivalent to the large changes observed for the sling-constraint and task-practice and sling-constraint and task-shaping groups from our laboratory. Other modifications have been made to the sling plus shaping intervention to enable treatment of: patients with chronic stroke with lower pre-

treatment levels of arm function than the patients in the CI therapy studies described above (4); persons with sub-acute stroke in pilot work in 6 laboratories that has served as the basis for an ongoing, multi-site randomized clinical trial of CI therapy; patients with acute stroke (15) (personal communication: Ro T, Noser E, Boake C, Wallace RB, Gaber M, Speroni A, et al. Cortical reorganization and motor recovery after Constraint-Induced Movement therapy in acute stroke); adults with traumatic brain injury (4); and children with cerebral palsy (66–68) (personal communications: DeLuca S, Echols E, Ramey SL, Taub E. Constraint-Induced Movement therapy in pediatrics: case study involving two therapy epochs; and Taub E, Ramey SL, DeLuca S, Echols K. Efficacy of Constraint-Induced (CI) movement therapy for children with cerebral palsy). In addition, the CI therapy approach has been extended to treat: lower extremity deficits in persons with stroke, spinal cord injury, and fractured hip (4); disordered finger movements in musicians with focal hand dystonia (3, 69); and expressive aphasia in persons with chronic stroke (3, 70).

MAIN THERAPEUTIC FACTOR

The question arises as to the common factor or factors underlying the therapeutic effect in CI therapy interventions for stroke. Although most of the techniques involve constraining movement of the less-affected arm, two modifications of the basic protocol involving just intense use of the more-affected arm and no restraint of the less-affected arm (i.e. the shaping-only and intensive physical therapy interventions), as just noted, do not. There is thus nothing talismanic about use of a sling or other constraining device on the less-affected extremity. The common factor appears to be repeatedly practicing use of the paretic arm. Any technique that induces a patient to use a more-affected extremity many hours a day for a period of consecutive days should be therapeutically efficacious. This factor is likely to produce the use-dependent cortical reorganization recently found to result from CI therapy (12, 33, 34, 44, 45) (personal communication: Ro T et al.) and is presumed to be the basis for the long-term increase in the amount of use of the more-affected extremity. It is not the constraint in CI therapy that is important; it is the intensive practice of correct use of the more-affected extremity. The constraint can be considered an adjunctive procedure. Similar considerations apply to the applications of CI therapy for conditions other than stroke.

EFFECTS OF PROVIDING CI THERAPY ON AN ATTENUATED TRAINING SCHEDULE

Studies that make use of restraint of the less-affected arm but do not give concentrated, extended practice in use of the more-affected arm cannot be said to have validly administered CI therapy. Two studies in patients with chronic stroke (9, 21), one of which

has been discussed previously (9), suggest that providing "CI therapy" on an attenuated schedule yields a markedly reduced treatment effect. In the van der Lee et al. study (20), the treatment group received 6 hours of therapy for 10 consecutive weekdays and were asked to wear a sling and resting hand splint during therapy hours and the resting hand splint alone outside the clinic over the treatment period. However, the therapy provided was much less intense than in our laboratory. Training in the van der Lee et al. study (20) was provided in groups of four using "house-keeping activities, handicrafts, and games" (p. 2370). In contrast, CI therapy is typically administered on a one-on-one basis by a therapist who continuously monitors the patient's performance, provides positive reinforcement to the patient, and shapes the difficulty of the task upwards. In fact, van der Lee et al., who received training in CI therapy in our laboratory, were counseled before they left that the attenuated treatment they were planning would yield inferior results. Not surprisingly, the attenuated intervention produced a pre- to post-treatment change in real-world arm use that was approximately one-third the magnitude of the mean effect obtained in this laboratory. It should also be noted that the control group in the van der Lee et al. study received an intervention that did not differ sufficiently from the treatment group with respect to the main therapeutic factor, the intensity of training. The control group was given Neuro-Developmental Treatment (NDT) for the same number of hours per day (6) as the experimental group. This training schedule is much more concentrated than is typical clinically or has been reported in the literature for NDT. Thus, this study neither implemented the treatment adequately, nor possessed an appropriate reference group for evaluating the effects of CI therapy.

Another study that reports a reduced treatment effect for CI therapy relative to the results from other laboratories also provided training on attenuated basis (15). Moreover, the study was carried out with patients with acute stroke (CI therapy was begun 7-14 days post-event). Thus, this study is of questionable relevance for evaluating the efficacy of CI therapy in general, as comparing the effects of a rehabilitation treatment with acute patients to its effects with chronic patients is a case of comparing apples to oranges.

CONSISTENCY OF CI THERAPY EFFICACY WITH GENERAL CLINICAL EXPERIENCE

In 1979, Andrews & Stewart (71) published an article entitled "Stroke Recovery: He Can but Does He?" To quote their abstract, "It was found that there was a difference in what the patients could do in the unit and what they did do at home. Each activity of daily living was less well performed in the home situation in 25-45% of cases" (p. 43). Most clinicians recognize the veracity of this statement. Indeed, decrement of performance outside the clinic environment is often reported as a source of intense frustration. The clinician works with a patient intensively for one or

more sessions with the result that there is a substantial improvement in some aspect of movement. However, by the time of the next therapy session, there have been varying degrees of regression and the degraded pattern of movement may have returned toward its original form. In fact, some clinicians report that they sometimes see the regression as the patient crosses the threshold into the corridor just outside the therapy room.

Surprisingly, very little explicit attention has been paid to what patients "[actually] do" outside the laboratory or clinic setting. A reasonably intensive search of the literature failed to reveal a single reference to this phenomenon; the Andrews & Stewart paper (72) has been virtually lost in the literature. However, for many patients there is undeniably a substantial discrepancy between motor performance in the clinic or laboratory and the actual amount of extremity use in the home. This gap may be viewed as an index of learned nonuse. CI therapy operates in this window. It provides a bridge between the laboratory or clinic and the life setting so that the therapeutic gains made in the clinic transfer and contribute to the functional independence of patients in the real world. In more general terms, CI therapy, which as noted earlier stems from basic research on the nature of movement with monkeys given deafferentation of a single forelimb, provides a bridge between the primate laboratory and the human stroke clinic.

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