

Constraint-induced movement therapy for chronic stroke hemiparesis and other disabilities

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Abstract. Constraint-Induced Movement Therapy (CI therapy) refers to a family of treatments for motor disability that combines constraint of movement, massed practice, and shaping of behavior to improve the amount of use of the targeted limb. CI therapy has controlled evidence for efficacy that supports its benefit for patients with chronic disability following central nervous system injury, regardless of their age or the interval since illness onset. Furthermore, the benefits transfer to real-world measures of limb use. Significant functional improvement may occur even after the patient has been treated with conventional physical therapy. In this paper we review the evidence for the efficacy of CI therapy, particularly for chronic stroke hemiparesis, but also for diverse other chronic disabling illnesses, including non-motor disorders such as phantom limb pain and aphasia. The adaptation of the therapy to the stroke clinic is described, along with a review of the neurophysiologic mechanisms that are postulated to underlie the treatment benefit (overcoming learned nonuse, plastic brain reorganization). Critical to the success of CI therapy is its modification according to disease factors, economic considerations, limitations of the practice setting, and the cognitive and physical status of the patient. We conclude by recommending future areas for research on CI therapy.

Keywords: Stroke, hemiparesis, rehabilitation, aphasia, phantom limb pain, transcranial magnetic stimulation

1. Introduction

This special issue of *Restorative Neurology and Neuroscience* details the neuroscientific foundations of promising new treatments for neurologic disability, especially with respect to purposive limb movement. Our research laboratory at the University of Alabama at Birmingham and its collaborating research groups have not only had the privilege to innovate diverse treatments for chronic functional impairment in a variety of disorders, but have also had considerable experience with transferring lessons learned from our investigational

approaches to the therapy clinic. We provide here an overview of outcomes from Constraint-Induced Movement therapies that were developed mainly from this laboratory and preliminary insights from our clinical experiences. Finally, we recommend future treatment studies that are based on our findings.

2. Constraint-Induced Movement therapy for chronic upper extremity hemiparesis following stroke

2.1. Justification for scientific research methods to innovate and revise rehabilitation approaches

Considered the leading neurologic disorder, stroke afflicts some 250 of every 100,000 persons in indus-

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trialized settings [43]. Post-stroke motor disability predicts enduring functional dependence [62] and impaired quality of life [10,35]. Presumably because the associated risks for injury or illness complications are considered paramount, motor deficit by itself is widely accepted by third-party payers to justify hospitalization for stroke rehabilitation (particularly when the lower extremities are affected), regardless of whether other disabling stroke deficits occur (e.g., aphasia, unilateral neglect).

At present, acute rehabilitation of hemiparesis following stroke involves selecting from among several approaches that have inadequate scientific testing (e.g., Bobath neurodevelopmental technique, Brunnstrom movement therapy approach, Rood cutaneous stimulation method, proprioceptive neuromuscular stimulation) [40,98]. Significant motor disability may persist despite standard physical therapy given in the acute stroke phase [37,68], yet until recently little has been done to assess sources of rehabilitation failure or to renovate the standard treatment approach. In addition, the prevailing but untested assumption among practicing physicians and therapists, at least in the United States, had been that functional improvement is unlikely beyond the first several months following stroke onset, at which time motor recovery has generally been thought to cease [36]. The chronic stroke patient had conventionally been thought to be unresponsive to therapeutic intervention.

Within the past few years, however, an increasing number of stroke clinics in industrialized nations have begun to offer *Constraint-Induced Movement Therapy* (CI therapy) to treat chronic hemiparesis, following the publication of successful controlled clinical trials in peer-reviewed journals (e.g. [78,85]). This rehabilitation regimen was developed from established principles of clinical research: (1) development of testable hypotheses concerning deficit and treatment response; (2) testing the hypotheses in an experimental animal model of the deficit; (3) transferring the treatment developed from the laboratory model to pilot controlled clinical trials in humans; (4) comparing experimental treatments with control interventions or repeated pre-treatment baseline measures; (5) using both laboratory measures and real-world functional outcomes to assess therapeutic efficacy; (6) conduct of a multicenter clinical trial to establish therapeutic reliability; and (7) revision and testing of treatment and evaluative methods to dissect the components that are crucial for therapeutic success.

The need to scientifically test therapies for stroke deficit becomes even more urgent in view of the an-

ticipated surge in the numbers of stroke survivors that will result from changing demographic factors [5,56], which in turn will strain economic resources for health care. Consequently, several alternate stroke interventions have recently been developed and are undergoing experimental assessment, including combining dextroamphetamine with standard physical therapy [20], treadmill training of gait with body weight support [54], and robot-assisted movement therapy [16]. Because these approaches are still early in their development, it is not yet possible to compare their efficacy to CI therapy. Consequently, we will limit our overview to CI therapy.

2.2. *The development of CI therapy for upper extremity hemiparesis*

Extensive research by Taub and colleagues showed that the chronic lack of use of the upper extremity induced in monkeys by unilateral sectioning of the dorsal cervical and upper thoracic spinal nerve roots (i.e., somatosensory deafferentation) could be reversed several months to years later with a physical restraint applied to the contralateral, unaffected arm (summarized in [76]). The restoration of purposive movement became permanent only after the restraint had been worn for at least 3 days. The precision of limb movements remained impaired, but the animals were able to resume bimanual self-care and routine daily living activities. Purposive limb use could also be induced when training was used, particularly the type termed *shaping*, which involves an incremental increase in the difficulty of task performance to achieve a reward [51,61,70,71,77]. In contrast, animals that had been bilaterally rather than unilaterally deafferented did not show as much motor deficit.

From these findings it was concluded that:

- 1) Functional limb impairment may be greater when neurological injury is unilateral, rather than bilateral, if motor fibers are intact in the affected limbs.
- 2) After unilateral neurological injury, the animal relies on the unaffected arm to perform basic self-care activities that had been formerly performed by either arm alone or both arms together (e.g., food gathering, locomotion, grooming).
- 3) Restricting the use of the unaffected limb for a fixed but short period can return functional limb use to the affected limb.
- 4) Training by shaping can also improve function in the affected limb, beyond restraint alone.

These observations led to formulating the concept of *learned nonuse* to account for part of the enduring limb motor deficit following certain types of neurological injury [75,76]. In this formulation, an affected limb may have a potential but unrealized ability to move due to reliance on the unaffected limb. In contrast, the absence of a functional imbalance between the limbs—as follows bilateral neurological injury—does not promote reliance on one limb for self-care activities. After unilateral neurologic injury, use of the affected limb for skillful movement can be re-acquired as a result of shaping tasks. In short, enduring nonuse of an affected limb may in part be behaviorally conditioned and maintained, rather than result completely in direct fashion from the neurological injury and the deficit's being unaffected by the individual's experiences with movement failure. Furthermore, because the functional impairment has been learned to a considerable extent, it can be unlearned. For evidence providing empirical support of this formulation see references [75,76].

These observations in turn led Taub [76] to propose that analogous behavior might occur in humans after other types of unilateral neurological injury, who therefore might respond to a similar treatment program. The proposed program would include:

- 1) restraining the less-affected arm;
- 2) shaping behavior in the training tasks given to the more-affected arm;
- 3) assuring that the patient would be able to understand and conduct training tasks; and
- 4) treatment provided by well-trained therapists who would motivate patients to participate.

Ince [26] and Halberstam et al. [22] had used one of the early training paradigms from the primate deafferentation research to produce improvements in the upper extremity movement of patients with chronic stroke. Shortly afterward, Wolf and colleagues at Emory University conducted treatment studies on chronically hemiparetic stroke and traumatic brain injury patients ($n = 22$) that were derived from one portion of the published CI therapy protocol [57,101]. In particular, their approach involved *forced use*, that is, restraint of the less-affected arm with a sling for 2 weeks while requiring the more-affected arm to conduct routine daily living activities, provided that the more-affected arm could initiate finger and wrist extension; they did not employ training of the more-affected extremity. The results indicated significant pretreatment vs. posttreatment changes in movement time and force on laboratory measures of movements typically used for daily

living activities. Movement quality, however, was reported not to improve. Benefits were measurable as much as one year post-intervention. The changes were small (effect size $d' = 0.2$), but they were reliable.

In 1993 Taub and colleagues [78] at our laboratory at the University of Alabama at Birmingham (UAB) employed the full treatment program proposed in 1980 [76]. (1) Chronic hemiparetic stroke patients ($n = 4$) underwent *massed practice* training of the more-affected limb for 6 hours/day for 2 weeks, while the other limb wore a sling restraint. Training tasks involved repetition of multiple activities typical of routine daily living tasks (e.g., playing dominoes, writing, throwing a ball). (2) A new outcome measure was used, the Motor Activity Log (MAL), which assessed real-world performance on numerous common daily living activities at home (e.g., opening a door, manipulating a wall switch to turn on a light). The MAL requires the patient to report on a scale from 0–5 the relative *amount* that the more-affected hand was used for each activity, and on a separate scale the *quality* of the hand's use on the same activities. The MAL shows no repeated measures effects in the absence of therapy [50], thus indicating good test-retest reliability. The MAL has concurrent validity with standard neurologic motor tests (NIH Stroke Scale, $r = -0.76$; Fugl-Meyer scale, $r = 0.85$) [11,28]. A laboratory measure initially developed by Wolf et al. and modified in our laboratory to include masked rating of quality of movement from videotape [78] was also used to directly assess maximal motor ability. This laboratory test has subsequently been termed the Wolf Motor Function Test (WMFT) and has been found to have high interrater reliability and correlation with other motor ability tests [32,52]. (3) A treatment control group of chronic hemiparetic stroke patients ($n = 5$) was included. These “attentional control” patients were encouraged to monitor their paretic limb and passively move it for brief periods with the less-affected limb, and they underwent standard range of motion assessments.

The results indicated that the treatment group had significantly improved performance on both the MAL and WMFT at the conclusion of therapy, while the control group showed no net gain over the same period. Furthermore, the treatment group showed an improvement (though nonsignificant) on the MAL for the two years following the treatment, while the control group again did not change. Real-world benefits extended both to amount of limb use and to quality of movement. Taub and colleagues [77] developed the treatment approach further by including the training tech-

nique termed shaping (see overview of experimental animal results earlier in this section).

These studies provided the essential basis for the current form of CI therapy: massed practice with the more-affected arm on functional activities, shaping tasks in the training exercises, and restraint of the less-affected arm for a target of 90% of waking hours. Through applying these measures for 6 hours a day for 2 weeks, the effect size on the WMFT was large ($d' = 0.9$), while for the MAL it attained an impressive $d' = 3.4$ [85]. Similar results were obtained when CI therapy was transferred to other laboratories [33,38,39,50,73,97]. The disparity between WMFT and MAL effect sizes probably reflects that CI therapy operates primarily on the gap between actual amount of spontaneous use of the more-affected extremity in the real world environment (as reflected by the MAL) and movement capacity when movement is requested in the laboratory (as reflected by the WMFT) [90]. Patients who appear to respond best to CI therapy are able to move their more-affected limbs to command reasonably well (thus showing that they have little to gain in movement capacity), but who habitually do not use their more-affected limbs in the real-life situation (i.e., spontaneous use of the more-affected limb is limited). These observations overturn the untested maxim that physical therapy is ineffective and hence unwarranted in the chronic post-stroke phase. Unpublished findings from our laboratory indicate no effect of either the patient's age or the chronicity of the stroke on the amount of treatment benefit.

Generally, the above findings have applied to patients with a substantial amount of pretreatment motor ability (i.e., at least 20° extension at the wrist and 10° in the fingers), but who use the more-affected extremity in the life situation very little. For patients with less active range of motion to command, the treatment benefit on the MAL is less (higher-functioning patients, mean change = 2.2 units; lower-functioning patients, mean change = 1.7 units) [85]. Furthermore, our laboratory has found that lower-functioning patients have reduced retention of training benefits over the long term, with a 20% reduction in MAL benefit by one year [84]. This result suggests that lower-functioning patients might benefit from a periodic re-administration of therapy. At present the value of post-treatment "brush-ups" has not been evaluated.

2.3. Concerns regarding CI therapy for the upper extremity

It is understandable that when a new therapy is said to considerably improve outcomes beyond standard care

and consequently becomes widely adopted, clinicians and clinical investigators regard such an advance critically. CI therapy continues to evolve in its methods and applications, and therefore we cannot anticipate here all concerns that may arise. However, we will address some of the more salient that have been raised.

2.3.1. CI therapy is nothing new [91]

CI therapy is a "therapeutic package" consisting of a number of different techniques. Some of them have been adumbrated before in neurorehabilitation, but as individual procedures and largely in reduced fashion. However, one does not find the use of restraint of the less-affected arm to constrain its assistance on daily living activities in standard therapy, and the application of massed practice of repetitive movements with one limb for several hours on consecutive weekdays for a period of weeks is without precedent. Shaping, consistent quantitative immediate feedback from performance, and the other behavioral procedures of CI therapy (e.g., behavioral contract with patients and with caregivers, home diary, objective recording and feedback to the patient of the amount of compliance with home practice) have been employed before though in an intuitive, non-formal manner and usually in isolated fashion. The main novel feature of CI therapy, though, is the combination of these different treatment components and their application in a prescribed, integrated, and systematic manner.

2.3.2. CI therapy is "more of the same," that is, an extended form of repetitive training that owes nothing to physical restraint of the less-affected arm [91]

As Taub et al. [84] had indicated, "there is nothing talismanic about use of a sling, a protective safety mitt, or other constraining device on the less-affected [upper extremity]," as long as the more-affected upper extremity is exclusively engaged in repeated practice. Indeed, the term "constraint" is meant to indicate that the general approach to overcoming nonuse or degraded use ("misuse") would be expected to be successful even with bilateral functional motor deficits or with lower extremity training, where a unilateral restraint would be impractical (as in fact, has been found to be the case) [77]. "Constraint" was not intended to refer only to the application of a physical restraint, such as a mitt, but rather to indicate a constriction of opportunity for the less-affected limb to be used exclusively for daily living activities, and a proscribing of the more-affected extremity from assuming a mostly passive role during

functional performance. For this reason, shaping is considered a form of constraint. For example, the requirement that performance be progressively improved for success to be achieved is viewed as constituting a very important constraint on behavior.

Preliminary findings by Sterr et al. [74] indicate significant treatment benefit on the MAL and the WMFT without using a physical restraint on the less-affected arm. While the long-term outcomes from their research have not been provided as of this writing, our own laboratory has evaluated either intensive practice or shaping to the paretic arm without physical restraint ($n = 9$) [53,85]. The findings indicated improved functional use by the more-affected limb, but there was a decrease by 2 years. The absence of a restraint is not inconsistent with the thesis of CI therapy, as discussed in the preceding paragraph. As a result, “behavioral” restraint (e.g., reminding the patient not to use the less-affected limb for training tasks) would be expected to improve use by the more-affected limb. However, if the special procedures used in this laboratory [53,85] are not employed, our clinical experience with stroke patients has suggested that routine reminders to not use the less-affected arm alone, without the use of a physical restraint, would not be as effective as the use of a restraint, particularly when patients may be cognitively impaired and therefore may fail to inhibit using the less-affected arm during the treatment interval. Consequently, we use the mitt to minimize the need for the therapist or the patient to actively limit use of the less-affected upper extremity, except when attending to personal hygiene or if the patient may be unstable during locomotion.

2.3.3. *CI therapy is unsafe* [58]

Concerns for the safety of CI therapy stem in part from the original form of the restraint, which was a combination of sling and splint [78]. However, in recent years our laboratory has modified the restraint, so that it now consists of a padded mitt that permits the less-affected upper extremity free movement for postural assistance when necessary, while still discouraging manipulation of objects that are to be used by the more-affected hand [81] (Fig. 1). In the experience of our laboratory and clinic, which have by now treated several hundred upper extremity patients, the use of a hand mitt has never contributed to injury. Concerns that more cognitively impaired patients may be unable to initiate protective reactions while wearing a mitt [58] have been addressed through incorporating cognitive exclusion criteria in the research program and careful

medical evaluation in the clinic, including asking the patient or caregiver about the frequency of falls. Patients with a history of recurrent falls are instructed not to wear the mitt during ambulation.

2.3.4. *CI therapy results in spurious improvement due to the Hawthorne effect* [100]

As the main real-world outcome measure of CI therapy, the self-report MAL may risk bias or artifact due to cognitive impairments that are not uncommon in stroke: impaired episodic memory, aphasia, or impaired abstraction. Our research laboratory uses cognitive exclusion criteria (normal performance on the Mini-Mental State Exam [18] and the Token Test [12]) to help increase participant reliability. In our CI therapy outpatient clinic, we use caregivers’ proxy reports on the MAL when patients appear unreliable. However, even cognitively intact patients may be vulnerable to the Hawthorne effect or experimenter demand, that is, improved performance or reported performance secondary to being monitored. Perhaps the patients overestimate their performance because of their desire to improve or to please the examiner, or as a nonspecific result of elevated mood due to positive reinforcement from the therapists, which would dissipate soon after program completion.

This concern seems less likely when considering that patients who received CI therapy in the initial study continued to improve on their MAL scores for 2 years afterward, while control subjects’ slight improvements during attentional intervention remained at baseline during the same follow-up period [78]. In subsequent research, patients who had received CI therapy were compared to a “general fitness control” placebo group of stroke patients who had been given strength, balance, and stamina training exercises, games to stimulate cognitive activities, and relaxation techniques [85]. The control group failed to improve on functional motor assessments, in contrast to the CI therapy patients, even though the control subjects had expected to improve, based on their responses to a pretreatment questionnaire, and also their posttreatment quality of life measures improved. These findings suggest that therapists’ social interactions with patients are not primarily responsible for functional motor recovery following CI therapy. Moreover, as we discuss in Section 2.3.6. below, we observed no difference in functional motor gains following self-administered CI therapy involving a workstation vs. standard CI therapy administered by therapists [41]. Thus, the amount of attention from



Fig. 1. A stroke patient undergoes CI therapy with the more- affected left hand, while the less-affected right hand wears a padded mitt.

a human observer does not appear to be crucial to CI therapy success.

A further challenge to the Hawthorne effect hypothesis is that outpatients in our CI therapy clinic who have already undergone upper extremity training frequently request to return several months later for lower extremity training as well, when appropriate. If the Hawthorne effect were responsible for the improved self-ratings of motor performance following CI therapy, one would have to hypothesize that such patients either had a psychological need for excessive medical attention or were deluded about their improvement when they requested further therapy long after program completion. These alternate explanations are unlikely, considering the time commitment and cost for CI therapy, including travel and other arrangements. It is more likely that after they returned home from the initial treatment program, such patients had sufficiently appreciated their improved upper extremity function to request further treatment. Indeed, among our patients were an air pilot who regained his pilot license and an ophthalmologist who returned to clinical practice, following upper extremity CI therapy.

It has also been claimed that daily assessment with the MAL during the CI therapy program may bias patients who become mindful of their previous scores as opposed to administering it only at pre- and post-treatment with a 2-week interval between administrations [100]. The argument is that the variability in score reporting may be constricted because of repeated assessment; the effect size of the treatment may there-

fore become magnified. However, our experience has been that when MAL assessments are limited to the beginning and end of treatment, response variability increases because the frame of reference for judging amount and quality of movement often shifts over a two-week period when the instrument is not administered, and the measure therefore has reduced consistency. Moreover, another aspect of the frequent administration of the MAL in this laboratory is that whenever a patient reports an alteration in one of the activities tapped by the 30-item questionnaire, the patient is asked a probing question in a prescribed fashion for whether that represents a real change. Since the large majority of such changes as treatment proceeds are improvements, most of the revisions in response are decreases in scores. This has the effect of reducing the size of the pre- to post-treatment change and thus the magnitude of the effect size.

The issue resolves itself empirically into the question of which schedule of MAL administration gives a more veridical picture of treatment change: once at pre-treatment and once at post-treatment with a 2-week interval in between as motor function improves, or more frequently with the added feature of using probing questions to determine whether the changes reported during treatment represent real alterations. The answer would appear to be provided by the results obtained through the use of two objective measures for quantifying real world arm use that have been developed in this laboratory: the Actual Amount of Use Test (AAUT) [90] and amount of movement of the limbs as determined

by accelerometers during most of the time when subjects are out of the laboratory and awake [89]. We have found that there is a large, significant increase in the ratio of more-affected to less-affected arm movement as a result of CI therapy, and that the change in this measure is highly correlated with MAL measures ($r = 0.77$ in one study and $r = 0.75$ in another, $ps < 0.001$) [88]. (These observations in addition provide further evidence against a Hawthorne effect.) The correlation between AAUT and MAL measures of CI therapy treatment change are similar (unpublished data). Accelerometry has at present become a standard part of the CI therapy regimen in the laboratory to improve quality assurance.

2.3.5. *The current format of CI therapy is too complex to appeal to stroke patients [58]*

A. Acceptability of CI therapy. Standard CI therapy for the upper extremity requires 6 hours of daily training for 2 or 3 weeks (depending on the severity of the deficit), exclusive of weekends, and wearing a padded mitt for 90% of waking hours. Page et al. [58] reported a survey of 208 stroke patients which indicated that two-thirds would be uninterested or unmotivated to adhere to the training requirements. However, the questionnaire used by those authors was unavailable upon request. Moreover, it seems unlikely that the patients were told about the benefits obtained by previous CI therapy participants. When this is done we have obtained very different results. Of 536 consecutive patients with chronic stroke identified by chart review [prior to the United States' Health Insurance Portability and Accountability Act (HIPAA) restrictions] and who contacted us in response to periodical and newspaper advertisements from 1995–1998 (before CI therapy was widely known), 5.0% indicated no interest in CI therapy treatment; in addition, 10.8% of the sample requested additional information, but were not contacted again (unpublished data). The remainder indicated interest in participating, though the amount of effort the therapy required was fully revealed to avoid the serious contamination of later dropout. Further, and perhaps more compelling are the data from the ongoing multi-site randomized clinical trial of CI therapy which involves 5 sites other than this one (see Section 6 below). Of 3,606 patients with subacute stroke contacted in screening, just 235 (6.5%) indicated that they were not interested in receiving the therapy [96].

B. Amount of treatment. Page et al. [59,60] reported significant improvements on the MAL, WMFT, and other motor measures following 3 hours per week of

combined standard physical and occupational therapy with a sling on the less-affected arm, distributed over 10 weeks ($n = 5$). The 30 hours of total treatment time were thus the same as would be encountered during standard CI therapy over 2 weeks. Page et al. suggested that their “modified” CI therapy regimen (which excludes massed practice and minimally uses shaping) would be more acceptable to stroke patients.

Similarly, as indicated above, Sterr et al. [74] obtained significant improvement following shaping of the more-affected arm for 90 minutes a day for 3 weeks, without a restraint applied to the less-affected arm. Sterr et al. contended that their treatment approach would be more palatable to stroke patients than would standard CI therapy.

At present, the optimal conditions for CI therapy are unknown. The 6-hour daily treatment amount was selected to accommodate therapist work schedules while still allowing extensive massed practice. Preliminary published evidence suggests that half the amount of daily therapy during 2 weeks may also be effective, but not as much as 6 hours daily [73]. Nonetheless, because stroke patients are prone to fatigue [27,48,93], it is conceivable that some patients would ideally be treated with less than 6 hours of daily treatment. However, there is probably a definite lower treatment limit for CI therapy to be effective. For example, in a recent study 10 minutes daily of repetitive movement training of the more-affected upper extremity for 2 weeks was found not to be functionally beneficial [99].

It remains to be seen whether the distributed treatment regimens proposed by Page et al. and Sterr et al. will be as beneficial as CI therapy concentrated over 2 or 3 weeks, since neither replication nor long-term outcome studies are available. Preliminary evidence from van der Lee et al. [92] suggests that the dilution of CI therapy through an increased ratio of patients to therapists and an attenuated requirement for repeated movement in hobby-type activities reduces the treatment benefit. This evidence indirectly supports a concentrated treatment program. It is also not clear whether CI therapy extended over 2 1/2 months would be as appealing for most stroke patients as would a 2-week treatment plan. Some patients might prefer to complete their therapy within 2 weeks rather than participate in an outpatient treatment clinic intermittently over several months, which might delay functional recovery. Furthermore, an extended treatment program might risk increased attrition, either due to lack of interest or to supervening medical comorbidities, to which stroke patients are especially vulnerable [2,66].

Numerous outpatient CI clinics in nonacademic centers in several countries provide the standard form of CI therapy. It therefore seems that there is a substantial demand for standard CI therapy, despite the objections raised by Page et al. [58].

Our CI therapy research program at UAB is conducting prospective trials to systematically vary the daily amount of CI therapy as well as the concentration of treatment (e.g., 2 weeks vs. 10 weeks, all treatment carried out in the laboratory vs. some carried out as monitored home practice). In this way we expect to learn what conditions will promote the greatest treatment response in the most patients. These findings should help patients to choose the treatment plan that would best suit them, if several alternate plans would be available. It is conceivable that stroke patients with enduring disability would favor the treatment program with the greatest promise for functional improvement, even if this would require intensive treatment over a short period.

2.3.6. The standard CI therapy regimen is unreimbursable in many current health plans [60]

This is currently true. At present, conventional physical therapy, which does not have controlled evidence for its efficacy, is nonetheless reimbursable, while in contrast treatment programs for rehabilitation that have controlled evidence for efficacy have not so far been approved. This appears to reflect a cautious approach from third-party payers, who await an unspecified critical mass of peer-reviewed publications, clinical trials, and other standards of evidence before approving a treatment that would be amenable to a very large number of patients with chronic stroke who are not otherwise being treated. The number of patients potentially involved would make the financial outlay substantial. However, in view of the economic burden currently imposed by stroke and the substantial increase in this burden due to the anticipated increase in the number of stroke survivors in industrialized societies, it would seem that third-party payers should favor therapy programs that are backed by controlled evidence for efficacy. Our laboratory is attempting to deal with the reluctance of third party payers to reimburse for CI therapy with its current research that systematically investigates dose-response profiles in CI therapy, as we indicated above, as well as evaluating the long-term economic benefits to patients and caregivers and the effect of using automated devices that reduce the use of costly therapist time to provide treatment.

In our laboratory's initial report of the latter line of research [41], carried out in collaboration with Peter Lum and others at the VA Rehabilitation Research and Development Center in Palo Alto, 9 chronic stroke patients were trained on a workstation called AutoCITE (Automated Constraint-Induced Therapy Extension) for 3 hours/day for 2 weeks and were compared with a matched group of 12 patients who received the same amount and concentration of standard CI therapy (i.e., with direct treatment from therapists). The AutoCITE device is a cabinet of several drawers, each containing implements for a different manual task that is computer-monitored through sensors mounted in the equipment. (Examples among the 8 activities include object flipping, letter tracing, and finger tapping.) Results indicated no significant differences between treatment groups; both showed effect sizes > 3.0 on MAL scores and equal to 0.5 on the WMFT. The findings are thus auspicious for reducing the time of participation of specially-trained therapists in this form of stroke rehabilitation. Evaluation of this approach in a more extended study might indicate substantial rehabilitation cost savings, which could favor reimbursement from health plans.

3. CI therapy for the lower extremities

The success of CI therapy for the upper extremity in stroke patients stimulated work in which the basic approach was adapted to treat functional impairments affecting the lower extremities. Gait disorders following stroke almost invariably involve hemiparesis. Learned "nonuse" should not appear importantly in ambulatory patients, who obviously must walk bipedally. Rather, gait patterns are slow, inefficient, unbalanced, and uncoordinated [86,102]. It is therefore more plausible to suggest that such patients have learned "misuse" [85]. In the same way that upper extremity patients become discouraged from using the paretic limb, hemiparetic stroke patients are also hypothesized to learn suboptimal gait patterns acutely following stroke without realizing an improved potential for more efficient use as a result of subsequent spontaneous recovery of function. Results support incorporating the CI therapy approach to train improved gait through intensive training on a treadmill, over-ground walking, stair climbing and shaping exercises involving the more-affected limb in various balance and posture transition exercises. Preliminary findings from a treatment group of 15 stroke patients indicated significant improvement

relative to control-intervention patients on several motor measures [79]. Further work with 21 additional subjects has confirmed the original results. Control was obtained (1) by administering this laboratory's upper extremity tests to the patients receiving lower extremity therapy as well the lower extremity tests of motor function, and (2) perhaps of greater interest by administering both upper and lower extremity tests to an equivalent number of patients receiving upper extremity CI therapy. Both sets of patients exhibited large gains in the extremity that was treated, but no significant improvement for the extremity not treated in the protocol. The lack of transfer of treatment effect from the lower to the upper extremity provides a useful control for many nonspecific effects associated with the treatment environment, including intensive interaction with a therapist. Over a 2-year period of follow-up testing, there was no decrement in retention of the therapeutic gain. Earlier, the laboratory of S. Hesse and K.H. Mauritz had shown that massed practice on a treadmill can produce substantial improvement in the gait of patients with stroke [24,25].

4. CI therapy for other disorders

The foregoing results indicate that the central nervous system in humans is amenable to recovery of functional performance through intensive practice and shaping following chronic motor deficit, as long as movement to command is possible. Similar results follow unilateral dorsal rhizotomy in monkeys (Section 2.2). These findings imply that it should be possible to functionally improve other disorders with intensive practice, constraint, and shaping. Our laboratory is actively examining the responsiveness of other patient populations to adapted forms of CI therapy. These results may help to direct future research in CI therapies. The following sections summarize our preliminary observations.

4.1. Traumatic brain injury (TBI)

As was indicated already, the study of Wolf and co-workers [101] using the restraint component of the CI therapy protocol [76] included TBI patients ($n = 5$). No differences in treatment outcomes were noted between the TBI patients and the stroke patients. Taub et al. [85] reported 3 chronic TBI patients who had undergone CI therapy. Two responded similarly to stroke patients. The third, who had bilateral motor deficits, was given CI therapy to each upper extremity in alternating

fashion. This patient improved but not as well as the other two. The lack of comparable benefit may have been because treatment to more than one limb during the same period diffuses the effect. Alternatively, bilateral motor deficits may reflect more extensive brain injury that reduces the capacity for motor relearning or brain reorganization. Our laboratory has continued to evaluate the outcomes of CI therapy for TBI and now has a series of 22 additional patients. For those two-thirds of these patients who adhered to the CI therapy protocol the treatment effect was as good as for patients with chronic stroke [69]. In recent work we have given 4 TBI patients CI therapy for the lower extremities to control for nonspecific effects on upper extremity function. Three of these individuals showed no improvement in upper extremity function, while one showed a moderate improvement. Three months after the lower extremity treatment they were crossed over to the upper extremity intervention. All four exhibited substantial improvement in upper extremity function comparable to patients with chronic stroke given upper extremity CI therapy as their first treatment.

4.2. Spinal cord injury

As indicated above (Section 2.3.2), bilateral central nervous system injury may theoretically respond to principles of CI therapy. Accordingly, patients with chronic paraparesis following spinal cord injury, who had retained movement to command, were treated with measures similar to those used to treat the lower extremities in stroke patients ($n = 5$) [83]. The patients responded better than did placebo or reduced treatment controls, with effect sizes above 1.5.

4.3. Hip fracture

Elderly patients with hip fractures may develop increased fear of falling [67] and secondary constriction of activity [103]. In effect, therefore, hip fracture may lead to learned nonuse or misuse of the lower extremities despite a non-neurologic etiology. Lower extremity training as discussed above has been undertaken with a sample of 5 hip fracture patients in our laboratory, with effect sizes above 1.5 [82].

4.4. Pediatric applications

As was indicated earlier (Section 2.2), the benefit of CI therapy for stroke hemiparesis is unrelated to the patient's age. Therefore, there would appear to be no reason a priori why CI therapy would not apply to children, after modification to accommodate age-specific behaviors. Our laboratory has found significantly improved performance on a pediatric version of the MAL and two laboratory motor function tests following therapy involving shaping and restraint in children with hemiparetic cerebral palsy [13,80]. A number of other laboratories have reported treatment benefits following use of one or the other of the main components of CI therapy in pediatric TBI, cerebral infarction, and cerebral palsy. However, when only one component is used, as in the case of adults, the therapeutic effect is substantially reduced [3,21,30,31,63,95,104].

4.5. Focal hand dystonia in professional musicians

Chronic massed practice with the fingers in certain manual occupations may lead to focal hand dystonia, a painless loss of control over individual fingers during task-specific activity, which results in co-contraction of flexors and extensors [49]. Musicians with performance focal hand dystonia have been shown to have a fused representation of the individual digits in somatosensory cortex, based on magnetic source imaging during tactile stimulation. In contrast, control subjects show greater individuation of the digit representations [4,15]. The cause of the altered somatosensory representation of the digits was undetermined, but it was suggested that repetitive practice (limb overuse, rather than nonuse) may somehow have been responsible. Similar observations regarding somatosensory cortex were obtained from owl monkeys following experimentally prolonged repetitive limb use [7]. Elbert, Taub and co-workers [15] suggested that interventions to individuate the somatosensory representations of the digits might reduce hand dystonia; this might be accomplished through repetitive practice of isolated digit movements, rather than the coordinated use of all digits that occurs during musical performance. Accordingly, Candia et al. [8,9], in collaboration with this laboratory, applied a variant of CI therapy to 5 musicians with dystonia, in which the single digit most disposed to dystonia underwent repetitive practice training over 8 consecutive days while one or more of the other digits were restrained with a splint. The results indicated significant post-treatment improvement in dystonia, and several of the musicians returned to professional performance.

4.6. Phantom limb pain

Patients may experience pain that appears to them to originate from the former location of an amputated limb or portion of a limb. The severity of such phantom limb pain is correlated with the extent of somatosensory cortical reorganization [17]. Since limb deafferentation (as follows amputation) is associated with somatosensory cortical reorganization [64], and since such reorganization occurs in phantom limb patients, then it might be possible to reduce the pain in amputees through increasing the amount of somatosensory input to cortical areas that mediate sensation for the involved limb. In collaboration with this laboratory, Weiss et al. [94] observed that amputees who wore a functional limb prosthesis ($n = 9$) that permitted extensive self-produced range of motion experienced significantly less phantom limb pain than did amputees who wore a more restrictive cosmetic prosthesis ($n = 12$). Although subjects in this study did not undergo CI therapy, the findings suggest that therapeutic measures that increase movement in the residual limb following amputation (and thereby, presumably, produce a use-dependent increase in the representation zones of the affected body parts) may reduce or prevent phantom limb pain.

4.7. Aphasia

Pulvermüller et al., in collaboration with this laboratory, suggested that aphasia may involve a linguistic form of learned nonuse [65]. That is, following acute failure to communicate effectively, aphasic patients may cease attempting to produce complex utterances and thereby rely on compensatory communicative channels (e.g., gesture, facial expression, modulated vocal intonation). Therefore, in a preliminary study 10 chronically aphasic patients underwent a modification of CI therapy, in which they played a language game where they requested cards with specific pictures on them from 3 other players (2 aphasic) while deprived of visual contact with them. Constraints were imposed by the requirement that they correctly name the objects on the cards or lose the game. Shaping was introduced by progressively requiring more complex and formal requests and by increasing the complexity of the items depicted (different colors, numbers and variety of objects represented on different cards and eventually on the same card). Treatment was 3–4 hours per day for 10 days; a control chronic aphasic group ($n = 7$) received 4 weeks of conventional aphasia therapy. The results indicated that the treatment group improved on most

standard measures of language performance administered, whereas controls benefited on only one measure. Furthermore, the treatment group improved on a linguistic analog of the MAL, the Communication Activity Log, while control participants did not improve. These findings were corroborated by another laboratory in smaller samples (total $n = 8$) of chronic nonfluent aphasic patients, using similar methods [44,45].

Unlike the research for upper extremity hemiparesis, comparatively few patients have been evaluated in these other treatment programs, and so further studies are needed before drawing conclusions on the ability to adapt CI therapy to other disorders.

5. Adapting CI therapy to the outpatient clinic

Since 2001 the present authors have supervised an outpatient CI therapy clinic at UAB, which has treated more than 150 patients as of this writing. As a result, our staff has gained experience with translating the laboratory experience to the practice setting.

To assure efficient operation, the clinic differs in several important ways from the CI research program at UAB. (1) The WMFT is not administered. The WMFT is a lengthy laboratory measure that is too extended to be a screening or outcome assessment in the practice setting. (2) Because the WMFT is not used, clinic therapists do not require patients to be linguistically proficient. Instead, therapists conduct short screenings (under 1 hour) of prospective patients, in part to determine whether they can follow task directions, whether spoken or gestured. A recent review of our records indicated that 9% of our patients were aphasic but nonetheless were able to complete the treatment program. (3) The clinic treats both upper and lower extremity hemiparesis, sometimes in the same individuals. In our laboratory's experience, results have not been ideal when more than one limb was treated simultaneously in a patient. Therefore, patients who request therapy for both the upper and for the lower extremity are treated serially rather than simultaneously. We currently treat upper extremity paresis for 2 or 3 weeks, depending on the severity, while lower extremity paresis is treated for 3 weeks. We allow several months of practice after the initial treatment before scheduling treatment for the remaining limb requiring therapy. (4) Although CI therapy has been investigated in brain-lesioned adults only when stroke or traumatic brain injury were the etiologies for hemiparesis, our clinic does not exclude other non-progressive brain illnesses. Consequently,

we have treated chronically hemiparetic patients following invasive treatments for brain tumor or cerebral vascular malformation. In our experience, these patients have behaved like stroke patients and responded as well. (5) The status of patients as reflected in MAL scores is monitored daily and problems in treatment are discussed as they arise. In addition, quality assurance meetings are held biweekly with staff therapists (who include both physical and occupational therapists) to collectively review individual patients' progress on the daily MAL scores and, through personal observations, to identify behaviors or other circumstances that may hinder treatment progress. Sources of interference are identified by consensus and plans are formulated to improve treatment procedures and compliance.

The screening process starts when the clinic's therapists communicate with prospective patients by telephone, e-mail, or regular mail. Because most of our clinic patients are not from Birmingham, medical and motor screening must be thorough to minimize inconvenience from traveling long distances to UAB. The therapists review the patients' motor abilities and medical histories, and ambiguous medical issues are discussed with the clinic's physician (VWM), who may require the patients' detailed medical records for review or discussion with the patients' personal physicians.

Subsequently, patients who are provisionally considered appropriate for treatment undergo comprehensive on-site medical examination by the clinic physician and detailed movement evaluation by an occupational therapist and a physical therapist. Total evaluation time is about 90 minutes. Because most physicians are unaware of the procedures in CI therapy, we require medical approval by the clinic physician rather than the patient's personal physician. In rare cases where poorly controlled conditions such as hypertension, cardiac ischemia, or epilepsy are encountered during medical screening, the clinic physician arranges with the patient's personal physician to improve control before clearing the patient for CI therapy.

Whether CI therapy programs in general will require an on-site physician, as ours does, is unclear but may depend on the clinic's geographic catchment area. A CI therapy clinic that enrolls patients primarily from the local population may refer patients with acute illnesses back to their primary care practitioners, if necessary, but this is not feasible in a program such as ours, which has a worldwide enrollment. An advantage to having a dedicated, on-site clinic physician is that unexpected medical complications can be addressed rapidly, in part because the physician has already evaluated the patient

and thus has a baseline for comparison. We rarely encounter unexpected illness in our patients, due in large part to our thorough screening measures. However, it should be noted that because stroke mainly afflicts the elderly and frequently results from chronic systemic vascular disease, patients in adult CI therapy programs may have age-related or cardiovascular comorbid illnesses that can unexpectedly worsen (e.g., congestive heart failure). Consequently, immediately available comprehensive medical services should be considered essential.

6. Improving the transfer of CI therapy to the practice setting: EXCITE (a multi-center randomized clinical trial) and other studies

This laboratory has helped set up CI therapy laboratories in Germany and has collaborated on studies with them that have obtained results that are quantitatively similar to those obtained here [34,50,73]. Aside from this work, it was unclear how well the methods that were developed here might transfer to other settings. One program has published preliminary findings following CI therapy for upper extremity hemiparesis, but without employing the ratio of therapists to patients and the intensity of treatment used here [92]. It was not surprising that the treatment benefit was much less than under more carefully controlled conditions.

To help determine whether the effects of standard CI therapy for upper extremity hemiparesis can be replicated at other facilities, our laboratory is collaborating in the first multi-center national randomized clinical trial of rehabilitation for upper extremity hemiparesis [96]. This effort is known as the EXCITE trial (Extremity Constraint-Induced Therapy Evaluation) and involves the participation of several institutions (UAB, Emory University, University of Southern California, Wake Forest University, University of North Carolina at Chapel Hill, Ohio State University, University of Florida at Gainesville, and Washington University). The training of personnel at the other institutions was carried out in two workshops here and fidelity to the standard testing and CI therapy training procedures is maintained by a formal scoring of periodic videotaped tester and trainer performance by the Training Center of this institution (David Morris). The object of the trial is to present upper extremity CI therapy in a single-blind partial crossover design. The patients are in the subacute phase (primarily 3–9 months post-stroke) and therefore differ from the mainly chronic population

treated here previously. Participants are randomized to receive 2 weeks of CI therapy or in the control group whatever standard treatment, if any, they choose to obtain. The control subjects are crossed over to CI therapy one year after their initial testing. Blinded motor and functional evaluations occur at 12 months post-stroke onset. This study will not only provide additional information about how well a specific CI therapy method may be transferred to other settings, but also whether providing treatment within the first year of stroke onset offers any therapeutic benefits over treatment after the first year. As of this writing, the total study enrollment consists of 222 stroke patients. Initial findings from this project should be available in 2005. Project details have been published [96].

7. Mechanisms for CI therapy benefit

Two non-exclusive mechanisms may underlie the treatment benefits from CI therapy.

7.1. Overcoming learned nonuse

The learned nonuse model of chronic hemiparesis developed by Taub (summarized in [76]) is based on a series of experiments carried out by him and co-workers with monkeys given surgical abolition of somatic sensation of a single forelimb by complete cervical and upper thoracic dorsal rhizotomy. The model is predicated on the fact that there is a loss of afferent drive to the motoneuronal pool innervating the deafferented limb in the early post-operative period, making use of that extremity difficult and for most functional purposes impossible. The sustained unilateral limb use failure would result in punishing interactions with the environment.

Thus, animals that attempted food gathering, locomotion, etc., with the affected upper extremity in the acute post-operative period would be confronted with inefficient or potentially inimical results. This movement failure transfers responsibility for all upper extremity functional activities to the unaffected contralateral limb, which is at least partially successful and is therefore rewarded.

Latent recovery of the potential for purposeful movement by that limb would occur spontaneously over several months. However, because the animal does not attempt movement with the deafferented upper extremity after the initial period of punishment, the latent motor

ability is not expressed, but is instead held in a powerful conditioned inhibition.

However, this latent potential is unmasked by the restraint to the contralateral upper extremity. Even so, the animal does not re-use the affected limb in the unrestrained condition until at least 3 days of restraint have occurred. Again, this would appear to reflect the powerful conditioned inhibition influence of the initial negative interactions with the environment. The learned nonuse of the single deafferented forelimb can also be overcome by training procedures, particularly the method termed shaping [76,77]. Experimental evidence providing support for this formulation may be found elsewhere [76].

At least two different learning mechanisms may underlie the motor deficit after stroke and its remediation by CI therapy. First, conditioned inhibition of movement is thought to occur following stroke and contributes to hemiparesis. Conditioned learning is a non-cognitive process (i.e., occurs without requiring awareness) [29] that in the case of stroke hemiparesis results from failed or ineffective movement attempts. Following the application of CI therapy, the balance of the contingencies of reinforcement are changed. Previously a stroke patient could get along at least to some extent in the life situation by using just the less-involved upper extremity. However, by restraining use of the less-affected arm and requiring the performance of various functional tasks, the stroke patient is placed in a situation where he either uses the more-affected arm or is rendered essentially helpless. This overcomes the learned nonuse. Through massed practice, these changes are strengthened and still further weakens the conditioned inhibition that was responsible for nonuse. Second, we believe that a slower, separate process of motor or procedural learning [29] occurs, in which the patient gradually develops new ways to move effectively. Following the intervention of CI therapy, the more-affected limb's movement on functional activities is modified through shaping by the therapist. While overcoming learned nonuse through the lifting of conditioned inhibition is likely the basis for increasing the amount of real-world limb use, as reflected by the rapid changes on the MAL following the start of CI therapy [78], motor learning is probably more responsible for improving movement quality and increasing the range of motor capacity (Section 2.2), perhaps in part through adopting compensatory movements, as reflected by the improved performance on the WMFT.

At this time we have only indirect evidence for the contribution of learned nonuse to sustained hemipare-

sis in humans, which most commonly appears following stroke. In addition, varying degrees of initial unilateral failure of purposive limb movement may occur acutely, i.e., anything from mild limb apraxia (select failure of skillful tool use) to complete hemiplegia. Furthermore, other motor and sensory hemisyndromes may be present, including spasticity, incoordination, and hyperkinetic limb movements (e.g., tremor) [19]. It is hypothesized that these diverse phenomena inhibit functional limb use. Thus, even though the patient may have a retained ability to move purposefully with the more-affected limb, which he may even acknowledge, he may not do so because of accompanying effort, clumsiness, or embarrassment. Thus, regardless of the extent to which subsequent latent motor recovery might occur (for which there is a great need for further investigation), the stroke patient with a sensorimotor hemisyn-drome often may manifest the performance-vs.-capacity inequality that we referred to earlier (Section 2.2).

It is noteworthy that this functional mismatch has not garnered much notice from stroke investigators. Beginning with the seminal investigation of Twitchell [87], motor recovery following stroke has been evaluated primarily by movement to command, while the comparative amount of spontaneous movement has seldom been examined. However, in 1979 Andrews and Stewart [1] noted that chronic stroke patients who attended an outpatient rehabilitation clinic often used the more-affected limb more in the clinic than their caregivers reported them to do at home. To our knowledge, this was the first (and only) published indication that movement to command (i.e., movement ability) could be discrepant from self-initiated limb use in the real world environment in chronic stroke. The consequence of this finding is that determining the extent of maximal movement ability in the clinic or laboratory following stroke cannot be accepted as a proxy measure for real-world performance.

In our clinical experience, this performance-vs.-capacity disparity can be extraordinarily large. As we indicated above, patients who appear to respond best to CI therapy have minimally impaired motor capacity (as assessed by movement to command), yet desire rehabilitation because they do not habitually use their more-affected limb (as indicated by their responses on the MAL). When shown the extent to which they can move and then asked why they do not spontaneously use the limb more often during routine daily living activities (e.g., turning on a light switch, opening a refrigerator door), they sometimes state that they understand

that they can perform these movements, but these are effortful and they must “think” about them. In contrast, activities performed by their less-affected upper extremity are habitual. Other patients have little or no awareness of the potential motor performance of which they are capable.

Through a mechanism that is incompletely understood but that may in part involve plastic brain reorganization (discussed in the next section), CI therapy reduces the “activation energy” to move the more-affected limb in routine daily living activities. Patients often tell us after a few days of the intervention that movements by the more-affected limb demand less of their attention and even occur without their realizing that the more-affected limb had accomplished the task (e.g., using a fork) until after the task was completed. At the same time, motor ability as shown by the WMFT also improves, but not as much as the improvement seen on the MAL. Thus, patients who benefit from CI therapy are generally not cured of their hemiparesis but instead gain significantly more spontaneous limb use than before treatment.

7.2. *Plastic brain reorganization*

Considerable research in laboratory primates by Merzenich and co-workers had demonstrated use-dependent remapping of motor associated cerebral areas (summarized in Mark and Taub [47]). Subsequently, Liepert and colleagues, in association with this laboratory [38,39], evaluated the changes in cortical motor representation with CI therapy. They used transcranial magnetic stimulation (TMS) to map the cortical motor representation of the abductor pollicis brevis (APB) muscle in the contralateral hand, as assessed by the peripheral recording of motor evoked potentials through surface EMG electrodes. Their findings demonstrated close to a doubling of the area of the APB representation in the infarcted hemisphere following upper extremity CI therapy, with significant medial or lateral shifts in the amplitude-weighted centers of activation. MAL changes with CI therapy occurred in parallel with the TMS changes, while values for either clinical or electrophysiological measures did not change during repeated pretreatment assessments. The findings suggested that a training-dependent change in motor cortex excitation or recruitment of additional motor areas had occurred. In a related study, Kopp et al., in association with this laboratory [33], recorded anatomical shifts in the dipole modeling of movement-related neuroelectric cortical potentials following CI therapy

in a small patient sample. These changes occurred only with potentials associated with purposive movements of the more-affected hand.

These observations suggest that two different but related mechanisms are involved with overcoming learned nonuse in stroke hemiparesis. Stroke that is acutely associated with effortful or ineffective purposive movement may chronically discourage or inhibit patients from further movement attempts, even when latent motor recovery has occurred. Simultaneously, contralateral limb use is increased relative to the pre-morbid state. The findings from Liepert et al. [38,39] suggest that the pre-CI therapy period is associated with reduced motor-associated areas for purposive movement by the more-affected limb. Following CI therapy, the expansion of the motor area associated with the more-involved limb coincides with its improved spontaneous use. Use-dependent brain reorganization is probably fundamental to the reduction in perceived effort and the increased use of the more-involved limb, since patients with limb nonuse do not readily improve performance simply by deciding to increase moving the more-affected limb without massed practice training or shaping.

8. Prospects for future research

It is readily evident from the foregoing that much work is needed to confirm the treatment effects that have been measured following the application of the CI therapy approach to conditions other than stroke, at least in part because of small sample sizes and the minimal attempts at replication by other laboratories. We would in addition like to indicate here some foreseeable extensions of investigations of CI therapy.

8.1. *Extending the research to more representative stroke samples*

Until the present, most research on CI therapy has recruited patients who have met strict criteria with respect to time since stroke onset, maximal motor ability, cognitive performance, and illness etiology. The current multi-center EXCITE trial will help to indicate the benefits of CI therapy as early as 3 months after stroke onset. If the benefits were to approximate those found in patients at least one year post-stroke onset, this would be of interest in determining how soon after stroke onset the therapy could be successfully introduced. However, it is likely that important administrative decisions

would be needed if CI therapy were carried out in the acute stroke period. In particular, could several hours per day be allowed to train improved limb use? The medical instability and more severe cognitive deficits of acute stroke patients might limit the amount of massed practice training that would be feasible. In addition, one would need to decide what priority should be given to standard stroke therapies, including occupational and speech therapy. Without a restructuring of the delivery of services, there would appear to be insufficient time in the patient's day to address the various disabilities that are commonly treated in acute rehabilitation.

Dromerick and colleagues [14] evaluated acute stroke inpatients with normal cognitive scores on the NIH Stroke Scale [6] following an attenuated form of CI therapy that involved 2 weeks of standard occupational therapy for 2 hours a day, directed primarily to the more-affected arm. The patients also wore a padded mitt on the less-affected hand for an additional 6 hours a day. This limited intervention resulted in significant improvement on a measure of commanded motor performance (the Action Research Arm Test [42]) but did not benefit standard functional activities assessments (the Functional Independence Measure [32] and the Barthel Index [46]). These findings are difficult to compare to standard CI therapy for subacute or chronic stroke patients because the investigators did not use comparable outcomes measures. Thus, it is not yet clear whether standard CI therapy may be accommodated in the acute stroke phase. However, on a research basis it would be of considerable interest to determine the magnitude of the treatment change that could be produced by the administration of different amounts of CI therapy.

Upper extremity CI therapy has been primarily developed for individuals who can purposively grasp and release objects, at least to some extent, since these movements are central to massed practice training and shaping. At present it is unknown what proportion of the chronic stroke patient population may meet these criteria, as well as other inclusion criteria. In a small study ($n = 56$) of upper extremity motor recovery after stroke [23], 17% of patients remained unable to appreciably squeeze a dynamometer by 3 months post stroke onset with the more-affected hand, while 30% had no function on the Frenchay Arm Test. Most of the remaining patients would presumably meet the active range of motion criteria that identify patients found to be amenable to substantial improvement from CI therapy. In the EXCITE trial [96], 6% of the total patients contacted (total $n = 3626$) met all inclusion criteria;

15% were excluded due to too high motor function, while 11% were motorically too impaired to participate. The remaining 68% of patients screened were excluded for miscellaneous other reasons (e.g., medical or cognitive problems, unable to complete assessment due to scheduling difficulties, post-stroke interval greater than 12 months, etc.) These studies do not allow determination of the exact proportion of chronic stroke patients in general who would be suitable for CI therapy in the clinic. However, given that stroke is the leading neurologic disorder [43], stroke prevalence in the United States alone exceeds 2 million [55], and motor deficit is a major source of chronic stroke disability [62], even if only a minority of stroke patients qualify for CI therapy, it would still be appropriate for a substantial number of individuals in the practice setting.

It is conceivable that patients without purposive control over the hand but with retained or recovered proximal control in the more-affected upper extremity might also benefit from massed practice training and shaping. In the absence of purposive hand movement, improved proximal control could well benefit activities such as feeding, dressing, postural stabilization, and bed mobility. Therefore, the responsiveness of patients with the least amount of motor control to intensive training deserves attention. Our laboratory plans to address this issue in the near future.

Strict cognitive exclusion criteria have been generally used in CI therapy studies. However, as is evident when observing acute stroke patients undergoing conventional rehabilitation, patients with cognitive impairments may nonetheless still participate in therapy. The minimum level of cognitive ability that would permit successful task performance in CI therapy has not been established. Our laboratory is presently evaluating the predictive value of certain cognitive evaluations (language, sustained attention, verbal memory, emotional stability) with respect to treatment outcomes, to help indicate criterion levels of cognitive performance essential to significant and sustained improvement.

As was indicated earlier (Section 5), our CI therapy outpatient clinic enrolls patients regardless of the etiology for cerebral illness, provided that they have non-progressive hemiparesis and limb nonuse. However, formal trials of non-stroke brain disorders (e.g., tumor resection, vascular malformation) in response to CI therapy have not been performed. In addition, studies have not thus far examined the specific consequences of multiple cerebral infarctions on treatment outcomes. Our laboratory is prospectively evaluating neuroimaging variables in relation to functional recovery, including lesion volume, location, extent of atrophy, and extent of white matter pathology.

8.2. Economic impact of CI therapy

As we indicated earlier (Section 1.3.6), CI therapy in its standard, concentrated format is not covered by most health care reimbursement plans. Although patients may realize significant functional improvement following treatment, this alone may be insufficient to alter insurance coverage. Consequently, studies should address to what extent CI therapy may return patients to the workforce (which indeed does occur, as we indicated in Section 1.3.4), or their caregivers' return to work. Our laboratory is now evaluating the social impact of CI therapy in this respect. It also is conceivable that improved mobility that follows CI therapy could reduce stroke-associated comorbidities (e.g., pressure ulcers, urinary tract infection, deep venous thrombosis, depression). Large-scale studies would be necessary to evaluate the extended health benefits of treatment.

8.3. Treatment of other illnesses

Although CI therapy was developed to treat non-progressive chronic illnesses associated with nonuse, it is possible that the approach might also benefit progressive diseases over shorter periods, which may improve the quality of life and reduce medical comorbidities. One progressive disorder with some symptoms that particularly resemble nonuse is Parkinson disease, which is characterized by reduced spontaneous movement that nonetheless improves with environmental stimulation (e.g., visible floor patterns, emotional arousal [72]). The disorder often progresses slowly enough that treatment benefits might remain over several years. At present the disorder is managed primarily by medication or surgery, and thus an improved physical therapy intervention could have considerable advantages. Similarly, multiple sclerosis in some cases might progress slowly enough as to be amenable to CI therapy. In either illness, preliminary studies regarding the extent of nonuse would be needed before pilot treatment trials are undertaken.

8.4. The shaping of CI therapy

It is obvious that numerous investigations based on the CI therapy approach are warranted, and our suggestions for research avenues are far from complete. It is most important to recognize that modifications of the therapy itself should be tested. Optimal treatment amount and concentration are unknown, and whether a physical restraint is necessary for maximal benefit for

all patient populations has not been established. The relative contributions of massed practice vs. shaping also require more study. Although the amount of work to be done seems imposing, the rewards are an improved understanding for how the central nervous system responds to injury and practice. In the same way that nonuse responds favorably to shaping and massed activity, so should the therapy itself benefit from shaping and increased research attention.

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