Published in final edited form as:

Neurorehabil Neural Repair. 2007 ; 21(1): 3–13. doi:10.1177/1545968306297329.

Confounders in Rehabilitation Trials of Task-Oriented Training: Lessons From the Designs of the EXCITE and SCILT Multicenter Trials

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Abstract

Two multicenter randomized clinical trials (MRCT), the Extremity Constraint Induced Therapy Evaluation (EXCITE) to improve upper extremity function after stroke and the Spinal Cord Injury Locomotor Trial (SCILT) to enable functional walking after incomplete spinal cord injury, demonstrate that complex, task-oriented physical therapies can be studied using a scientific methodology during inpatient or outpatient rehabilitation. In the past, a new therapy's benefit may have been overestimated by comparing it to no treatment or to a conventional treatment at a low intensity of practice. Sample sizes were often too small and may have failed to detect the efficacy of a new intervention. In addition, whereas statistical significance in outcomes has been critical to understanding whether one treatment is better than another, the clinical significance of outcomes must also impact the interpretation of the results of a trial. MRCT designs will continue to improve through attention to the limitations of preclinical animal models that offer a conceptual basis for the treatment from enrichment strategies at every phase of trial development from more vigorous dose-response studies using adaptive methods by capturing interim measures of behavior and functional neurophysiologic adaptations during the treatment phase by aiming for a clinically meaningful control intervention and by including ratio or interval outcome measures when feasible that capture a target of the intervention in relation to gains in daily functioning and quality of life.

Keywords

Rehabilitation; Stroke; Spinal cord injury; Randomized clinical trials; Treadmill training; Constraint induced movement therapy; Hemiplegia; Paraplegia; fMRI

For a long time, progress in neurorehabilitation proceeded like the anxious fellow who drives his car by taking his foot off the brake. Two of the first foot-on-the-gas-pedal runs were recently published. Multicenter randomized clinical trials (MRCT) for novel task-oriented interventions improved walking after incomplete spinal cord injury (SCI)¹ and increased upper extremity function in patients with hemiparetic stroke.² These trials gathered enough subjects who met entry criteria to demonstrate that the intervention could

be provided by many therapists in a similar fashion to produce similar results. By careful administrative management, the trials entered and kept enough subjects in each MRCT to determine the efficacy, effectiveness, and generalizability of each intervention for its intended sample of patients.

Every MRCT must, for practical reasons, limit what it can test drive. Every trial should, however, contribute to better designs. Future trials, at least in the United States, are likely to draw upon previously published designs,^{3,4} as well as explore ways to improve upon them. Some of the problems inherent in the recently completed MRCTs have solutions that can be incorporated into future phase I, 2, and 3 clinical trials. These enrichment strategies may also improve the fuel economy of a trial by reducing the number of subjects that are necessary to power an MRCT (Table 1).

The Extremity Constraint Induced Therapy Evaluation (EXCITE) trial^{2,4} for upper extremity function after stroke and the Spinal Cord Injury Locomotor Trial (SCILT)^{1,3,5} for walking after incomplete spinal cord injury (SCI) tested well-defined physical/occupational therapies. EXCITE compared *constraint induced movement therapy* (CIMT) to usual care. The therapy focused on functional use of the affected arm and hand in hemiparetic patients within 3 to 9 months after stroke. Entry criteria specified the amount of residual motor control of the hand and required patients to be able to stand for several minutes and perform independent toilet transfers. The intensity of training for the most compliant subject included 84 hours of formal practice in the 2 weeks of training with shaping and behavioral reinforcement, another 4 to 8 hours a day for 14 days (80 hours) of forced use of the UE while wearing a mitt on the unaffected hand, and recommendations for another 15 hours of practice monthly up to the 1-year final outcome measures. The control group in EXCITE received no formal training and had no interaction or instruction from a therapist, and no criteria were set for practice at home with the affected arm. This passively managed group was called “usual care” since the investigators believed that most patients in the United States would not continue to get treatment for a persistently paretic arm and hand beyond 3 months after stroke.

The SCILT compared treadmill training with partial body weight support (BWSTT) combined with overground training to an equal amount of only overground mobility training in patients admitted for inpatient SCI rehabilitation within 8 weeks of onset. Subjects had an incomplete injury (graded American Spinal Injury Association B, C, or D) and could not walk without maximal assistance at entry. All subjects received 12 weeks of their study-standardized inpatient and outpatient mobility therapy amounting to about 45 hours, in addition to routine rehabilitation activities.

In EXCITE, the CIMT group increased the speed at which it completed a battery of standardized tasks with the affected hand compared to the control group that did not receive any therapy. In SCILT, the BWSTT and control groups had equal outcomes at the end of therapy and at 6 and 12 months for level of walking independence, walking speed and distance, need for assistive devices, and leg strength. These trials added weight to the evidence of the few available RCTs that progressive, task-specific training of considerable

intensity for patients who have enough spared motor control can significantly improve outcomes relevant to the focus of what was practiced.⁶⁻⁹

The 2 MRCTs have much in common, so they can serve as a template-in-progress. They share the conceptual basis, drawn from animal and human behavioral and functional neuroimaging studies, that skills can be improved with task-oriented practice and reinforcement that induce cortical adaptations and representational plasticity. They build upon mechanisms for motor learning in prototypical behaviors such as reach-grasp-release or walking. Although it would be impossible to account for all cognitive-motor system interactions, CIMT and BWSTT techniques consider multimodality cues, goal orientation and feedback during practice, sensorimotor integration and mechanisms of efference copy to improve disordered movement, massed practice, and the motivation and rewards necessary for learning. Many small pilot studies of each intervention had suggested efficacy in highly selected subjects. Indeed, several of the investigators in each MRCT had spent a decade developing and test-driving the intervention. Each trial employed gadgets, such as a bank of items for upper extremity practice and a mitt for the unaffected hand or a treadmill and body-weight-support apparatus. Although these devices captured the imagination of patients, therapists, and the media, the physical and verbal cues provided during structured practice were the most important aspect of training in each trial. Their outcome measures, performed by successfully blinded observers, were tied to the expected effects of the intervention. These study design features had strengths as well as a few weaknesses that can be considered by future trialists when they put their foot to the accelerator.

PROBLEMS IN DEVELOPING AN MRCT

Animal Models of Treatment-Associated Behavioral Gains

Animal models of injury and recovery have contributed to an understanding of the possible mechanisms of rehabilitation-related gains. Do clinicians appreciate the potential limitations of these models before trying to translate laboratory experiments into the basis for an MRCT?¹⁰

Activity-dependent plasticity in many forms has been shown to parallel functional gains in animal models.¹¹ Drawing upon animal models to support a neurorehabilitation intervention is compelling, but the translation from an animal model to human studies can take many wrong turns, as trials in neuroprotection have revealed. Indeed, although the EXCITE and SCILT trials were characterized as being based upon animal models of recovery of limb function and walking,^{3,4} the relevance of the models to the thrust of the clinical trials may have been overdrawn.

Animal models have revealed a variety of biological effects in response to exercise¹² and an enriched environment.¹³ The behavioral deprivation of standard housing conditions for rodents may be so stressful and unstimulating, however, that any change in level of activity could alter gene expression and enhance synaptic efficacy for learning.¹⁴ Another confounder in the translation of animal models of rehabilitation interventions into human trials is that patients improve their mobility and self-care skills by using cognitive and physical cues provided by therapists. Rehabilitation strategies involve informed practice of

progressively difficult tasks that are of value to patients. Animal models are limited to simple behaviors acquired by reinforcers such as a sweet drink or food pellet. Also, the statistical versus “clinical” significance of a change in animal behavior on a standard test that cannot be compared to human behavior may degrade the lessons from a preclinical animal model.¹⁵

The basis for EXCITE was derived from several types of animal experiments. Taub had observed that somatosensory deafferentation of one forelimb of monkeys led to nonuse of that limb in daily activities.¹⁶ Forcing the animal to employ that limb by preventing use of the unaffected one led to greater functional use. The notion of learned nonuse that could be overcome by forced use was extended to patients after stroke who had motor loss and did not incorporate the hemiparetic hand as much as seemed possible. Sensory loss compensated by visual input and a training paradigm that rewards hungry monkeys for grasping a food pellet with the free but insensate digits seems a bit of a conceptual stretch when applied to patients with hemiparetic stroke who have limited motor control. Patients may also have cognitive impairments and practical reasons not to readily incorporate the affected hand. In the translation of the model to EXCITE, it is somewhat ironic that the CIMT intervention was compared to no treatment, which would presumably encourage nonuse of the affected hand.

The basis for BWSTT arose from the finding that thoracic spinal transected cats and rats could be trained on a treadmill to step so that their hindlimbs kept pace with the belt speed. The quadrupedal animals required some trunk support and stimulation by pulling on the tail to enhance extension of the hindlimbs. They did not become able to walk overground. Central pattern generation (CPG) within the lumbar motor pools, as well as the timing of sensory inputs that accompany loading and unloading each hindlimb while optimizing hip extension at the end of stance, became possible explanations for this stepping behavior and key features of the conceptualization of BWSTT.¹⁷ An emerging rehabilitation concept was to tap into the intrinsic spinal networks that generate alternating flexion-extension movements by supplying “appropriate” sensory inputs. If a spinal network for automatic reciprocal flexion-extension leg movements exists for bipedal walking, this polysynaptic system would give flexibility to supraspinal controls. The CPG and other spinal polysynaptic pathways, however, would be only one of many control elements for upright walking. The applicability of the spinal transection model to human studies of patients with hemiparesis and paraparesis, then, is uncertain. Although neurobiological hypotheses about spinal cord plasticity can be tested in this model,^{18,19} the loss of all ascending and descending pathways best serves as a model for complete SCI, not for stroke and incomplete SCI. The model may be of greater value for combining locomotor training by BWSTT with strategies for axonal regeneration or lumbar cord microstimulation. The animal studies, of course, were also performed only on a moving belt and without motor and cognitive cues and feedback during training to try to correct kinematic, kinetic, and spatiotemporal aspects of the gait cycle. Task-oriented training, however, that employs massed practice of stepping with cues and feedback for postural control, foot trajectory, kinematics, and other elements, did serve as another basis for the strategy of BWSTT. Both BWSTT and CIMT help patients find greater access to latent motor control by eliciting components of an action, then a more complete task-related action. Brain and cord-injured animals are not trained this way.

Pre-MRCT Pilot Studies

Pilot studies aim to define the intervention and look for responders. Can small trials of an intervention establish the likelihood that the intervention is worth the long road trip of an MRCT?

A review of the efficacy of 10 general types of physical therapies used to manage patients after stroke found modest gains for many of the strategies but pointed to the difficulties in interpreting the clinical effectiveness of any of the treatments.²⁰ A problem in interpreting meta-analyses and reviews of related studies in preparation for an MRCT is that the designs and methods usually differ considerably from one small trial to another. The experimental interventions may vary not only in the application of a particular strategy, but also in time of initiation, intensity of their application, and how they contrast with the control intervention. Convenience samples often constitute the study population, which leads to ascertainment bias. The control condition may be historical controls or no treatment or an A-B-A design in which carryover effects muddle the results. The interventions may have low statistical power to detect differences since outcome measures vary in their reliability as well as sensitivity and specificity for detecting clinically important changes. EXCITE and SCILT had to ride over the road bumps of pre-MRCT data.

Investigators who try to draw information from small trials as they plan larger ones would be helped by protocols that limited themselves to well-characterized populations, a few relevant outcome measures, explicit therapy procedures, and dose-response studies. These details are necessary to properly power an MRCT. For example, in planning the SCILT, the investigators found almost no walking outcomes in the literature up through 1999 that had been related to the initial ASIA grade, such as frequencies of different levels of independence, walking speed, walking distance, and assistive device use within 1 year of SCI,³ despite the fact that databases included thousands of patients.

Functional Imaging for Biological Plausibility

The finding that a physical therapy induces reorganization in ipsilesional and contralesional motor networks and within the representation for the hand or leg by functional magnetic resonance imaging (fMRI), or that it alters excitability within primary motor cortex (M1) by transcranial magnetic stimulation (TMS), has been taken as proof of principle about an intervention's fundamental action and utility. Are such changes meaningful enough to serve as roadmaps to an MRCT?

Patients and the media were drawn to a report that CIMT training had induced brain reorganization.²¹ These findings, however, do not reveal causality. Subsequent small studies reproduced or failed to show reorganizational changes using the EXCITE protocol.²²⁻²⁴ During the rehabilitation of patients with chronic stroke who meet criteria for CIMT, the combination of increased or decreased intracortical facilitation by TMS within ipsilesional M1, in relation to a decrease or increase in the blood oxygen fMRI signal, perhaps best reflects a change in synaptic efficacy with training. For example, when the pyramidal tract is injured enough to cause paresis, decreased TMS excitability and increased fMRI signal point to reorganization with recruitment of spared sensorimotor network regions.²²

Activation maps of fMRI voxel counts and TMS facilitation that contrast a baseline assessment to post-treatment include numerous biological and statistical assumptions. Direct brain-behavior correlations have not been made from these studies.²⁵ They capture a global snapshot of the consequences of many short and long-term events that may evolve during motor-skills training.²⁶ As noted on the left side of Figure 1, acute changes are produced by an activation paradigm during an fMRI or TMS study, but these also reflect the much slower adaptations driven by training and other endogenous and exogenous neural activities, including the neurobiological bases for skills learning. These changes, over time, could be used to reveal the stages of learning during CIMT, BWSTT, and other interventions.²⁷⁻³⁰ If consistent brain-behavioral correlations proceeded during repeated functional imaging studies with behavioral measurements over the course of a treatment, and did not occur in the control group that made significantly fewer gains, the argument favoring the utility of functional imaging to reveal that a network was engaged by a rehabilitation strategy and modified to improve motor control would become more tenable.

Sample Population

Inclusion and exclusion criteria, randomization, selection of subjects from multiple sites, and masking of outcomes lessen ascertainment bias and helps generalize results. Small studies at 1 site fish for subjects that add up to a convenience sample. These patients probably will not represent the characteristics of the full population for which the intervention was designed. MRCTs aim for prospective accrual of cases from a wide catchment. If the treatment works across therapists and clinics, it may work for everyone who meets the entry criteria. Who got into the EXCITE and SCILT trials?

The EXCITE investigators could not know much about the possible errors of omission and commission that may have affected the hemiparetic hand prior to the month before entry, such as a painful joint that lessened ongoing use. Patients were identified from more than 270 hospitals and likely had widely different prerandomization experiences in rehabilitation. Because SCILT subjects were identified on admission for their initial rehabilitation within an average of 4 weeks after onset, they were more likely to represent the typical population of patients with incomplete SCI at their stage of recovery.

The EXCITE trial screened 3626 patients who were 3 to 9 months poststroke to capture 222 (6%) for randomization. The reader may wonder about the percentage of patients who can meet its entry criteria. Aside from time since onset, one of the most difficult criterion to meet in finding subjects for EXCITE was the distinct upper and lower limit for motor control of the hand. Higher-functioning participants could voluntarily extend the wrist 20° with at least 10° of extension of each metacarpophalangeal and interphalangeal joint but not employ the hand during daily activities. Lower functioning subjects could extend the wrist 10° with 10° of thumb abduction and extension and similar extension of at least 2 more digits. The trial did not enter enough of the higher severity subjects to make conclusions about efficacy as comfortably as they could with the less impaired group. Smaller trials of acute use of CIMT found that about 10% of subjects admitted to an inpatient unit after stroke would meet the 20° entry criteria without being too highly functional.³¹⁻³³ EXCITE did not address the minimal motor control necessary for CIMT to be of value, differences

related to stroke lesion location, and the influence of neglect and visuospatial, language, praxis, or other cognitive impairments on the effects of the training strategy.

The SCILT screened 1434 admissions for SCI at 6 rehabilitation centers to obtain 155 who met eligibility criteria (10%). Most were excluded because they had a complete SCI or a medical problem that would limit mobility training. In retrospect, most entries had an incomplete cervical (ASIA C) SCI. ASIA D patients were kept in their community hospitals and not referred to SCI centers. The results cannot be applied to patients who are more than about 4 months beyond their SCI who still cannot walk at all or walk functional distances. Patients who were entered within 4 weeks of onset did better, not because their therapy began sooner but because they gained lower extremity strength over time and would have been entered as ASIA C rather than B or as ASIA D rather than C at 8 weeks, the maximum time for entry.⁵ This is the “noise” of spontaneous recovery during acute intervention, which tends to require a larger sample size. However, the results in SCILT were so robust that a futility analysis estimated that more than 2500 subjects would have to have been entered to determine if 1 intervention was superior to the other.

Experimental Intervention Versus Control

What is the proper control intervention for a task-oriented trial aimed at improving motor skills?

One could hardly ask for a greater contrast in the treatment styles, intensity, and focus between the active and inactive groups in EXCITE. Without doubt, task-specific practice enhances motor skills in normal subjects. Fundamental mechanisms of skills learning do not differ between healthy and brain or spinal cord injured subjects (Figure 1). The substrate available for learning may differ. The best comparison for future CIMIT-like trials ought to be a specific upper extremity therapy, if the intention is to demonstrate that the CIMIT strategy, rather than the availability of any intensive therapy, can improve outcomes. An intervention that encouraged functional gains but still represented a sharp contrast to the CIMIT approach would have helped clinicians interpret the full benefit of the EXCITE strategy. Instead, CIMIT was compared to a sugar pill—perhaps not even to that. No sweets were given to the untreated arm of the trial. The attention, encouragement, family support, and motivation, among other incalculable interactions, rendered the CIMIT group to become quite different than the control group. An uneven distribution of contact and involvement with subjects in each arm of a trial has clouded the results of many prior trials in rehabilitation. The EXCITE-equivalent control condition for SCILT would have been to keep patients in their wheelchairs and have them try to walk on their own, which would not have been ethical or clinically meaningful at their stage of rehabilitation.

In SCILT, the contrast between early initiation of repetitive practice with BWSTT versus more conventional training was negated by the same pattern of recovery of muscle strength of the legs in each group by 6 weeks after entry.⁵ Mobility improved in each group in relation to its ability to practice as motor control increased, presumably due to increases in corticospinal and other descending tract conduction in spared axons, along with skills learning.

Spontaneous Recovery

In EXCITE, improvements in affected UE function from baseline to the 12-month primary outcome measure were significant for each group, which suggests that the control group had not reached a pre-entry plateau. Gains in the control group that entered within 9 months of onset were attributed to possible spontaneous recovery. What is *spontaneous recovery*?

Gains that are not driven by practice and learning may evolve soon after onset of a brain or cord injury as neuronal excitability, synaptic function, and nerve conduction in spared networks recover from the sequela of ischemia, inflammatory molecules and cells, toxic effects of heme, downregulation of neuromodulators and receptors, collapse of dendritic spines, aberrant neurotransmission, and loss of transsynaptic activity. Endogenous repair processes may follow.³⁴ These cascades of change are not likely to play a role beyond a few months after onset of ischemic stroke or traumatic SCI. Gains seem far more likely to arise within the reorganizational activity of spared pathways—intentional and attentional drives for movement, unmasking of latent synaptic connections and greater facilitatory drive in spared ensembles of neurons near M1 and remote (premotor areas and homologous areas of the uninjured hemisphere, for example) from the injury,³⁵ learning through practice to fire selected motor units to make a desired if not kinematically normal movement to attain a functional goal, and other adaptations. Patients in the SCILT, for example, continued to improve beyond their 12-week intervention probably because they had achieved enough motor control to practice walking and to build endurance, not due to spontaneous recovery.

Interpretation of the Results

Clinicians and patients who do not carefully read the original study publication can misinterpret its results. Was EXCITE a success because it revealed efficacy, and was SCILT a failure because it did not detect a difference between 2 interventions?

The EXCITE intervention was designed for a very specific and rarified level of impairment and was only better than no treatment. The SCILT style of BWSTT was equivalent to a conventional approach that made sure that an hour of mobility training was given even to the least mobile subject. The null hypothesis was not rejected in SCILT. The reason was that both interventions led to clinically robust outcomes for those who regained the ability to walk and both failed to get the ASIA B subjects, who were most impaired, to walk. That is, overall, good news: Intensive treatments work if they are task-oriented and if the subjects are regaining motor control as the acute effects of the injury recede and the effects of training proceed. The results of the SCILT, however, are not relevant to ASIA B and C patients with chronic SCI. Limitations of a trial must be stated, as they were in EXCITE and SCILT.

SOLUTIONS

A focused task-oriented therapy that might show efficacy if its intensity were adequate may depend on many interactions. These include the study population, severity of the impairment and related disability that is in the headlight beam of the intervention, the proximity to onset, the rehabilitation and daily experience of subjects prior to entry, inadvertent crossover effects between the control and experimental intervention, and the contrast in type and

intensity of what the control group receives compared to the experimental group. Other recently mapped North American trials have looked at some of the design problems of studies like SCILT and EXCITE and are applying their solutions. These recent ongoing MRCTs include the Locomotor Experience Applied Post-Stroke (LEAPS) trial of BWSTT,³⁶ bilateral arm training with rhythmic auditory cueing (BACTRAC),³⁷ and the Veterans Administration Cooperative Study No. 558, robotic-assisted upper-limb neurorehabilitation in stroke patients.

Ideal Samples

By picking consecutive admissions to multiple regional rehabilitation centers, the SCILT sample likely reflected a real-world sample. The identification of patients in LEAPS occurs during admission for acute inpatient rehabilitation to one of the training sites. Poor walkers are identified early but are randomized only if they remain poor walkers at 2 (early entry) or 6 (late entry) months after stroke. This design feature provides a group at 6 months that, unlike in SCILT, has probably stopped making rapid strength and mobility gains. Unlike EXCITE, the LEAPS investigators will know the rehabilitation history and brain lesion location of their subjects. Subjects in LEAPS are also stratified for severity based on walking speed at the time of randomization. Thus, time from onset, experience, and levels of severity should produce well-understood arms for the trial.

Pretrial Dose-Response and Timing Studies

What is the right dose of rehabilitation at the right time after onset of paresis? In prior clinical trials of stroke rehabilitation interventions, an average of only 16 additional hours of therapy was provided for the treated group compared to the control group.⁹ The effectiveness of most of these interventions was very modest at this intensity.

A large MRCT should not be undertaken until a variety of doses of therapy (number of sessions, duration of sessions, duration of the program) have been examined and compared. In addition, the intensity requirement may differ depending on whether the subjects have very poor or moderately good residual motor control early or late after onset. More treatment time may benefit subjects who begin locomotor training with a walking speed of <0.4 m/s than who start at >0.6 m/s or who have 10° of residual wrist and finger extension compared to 20°. More therapy as well as more enrollees may be needed when a trial starts within 1 month compared to 6 or more months after onset, especially to demonstrate efficacy in the most disabled subjects. Clinical markers for the likelihood of gains are critical to identify a priori the population that is most likely to benefit from the experimental intervention at a particular time after injury and at the optimal dose.^{15,26,38}

Some patients who receive CIMT may make large improvements within the first 1 to 2 days of treatment. For trials that do not begin soon after onset of disability, a short phase-in of task-related therapy that is not the experimental intervention for all subjects for 6 hours could be instituted to determine whether the patients are reasonably stable in their affected arm function or walking ability prior to randomization. If no change occurs, then the investigators proceed with randomization. If more than a 10% to 15% change develops on

an interval scale (depending on its reproducibility), another short course may be necessary. This approach adds cost, but improves the validity of the results.

Adaptive designs, which have been used in drug trials, could provide real-time learning about dose-response relationships. For each intensity and duration of therapy, starting with the lowest, the investigator continuously reassesses the futility for further gains. Investigators can compare a fixed number of subjects at a fixed dose and increase intensity of therapy in blocks of subjects or enter a larger number of subjects that simultaneously receive 1 of 3 or more doses.

Components of the Intervention

Investigators may become wedded to the accessories and not the critical components of an intervention. Is a physical therapy's success equal to the sum of its parts?

EXCITE did not aim to determine whether any 1 component of the shaping, practice, and forced use strategy dominated the overall effectiveness of CIMT. Programs of mCIMT (modified or mini CIMT) have been proposed and tested. These employed shorter therapy times or no constraint of the unaffected hand in sample sizes too small to allow any conclusions. These related strategies may be studied within the context of cost versus benefit in the future.³⁹⁻⁴²

The SCILT and LEAPS trials gave therapists guidelines for progression of training by varying leg loading and walking speed, but the most efficacious components for managing stride length, cadence, and progression are unknown and may not matter. For example, walking speed may need to compromise between a slow pace that could engrain excessively slow walking overground and a belt speed that is too fast (eg, >3 km/hr) for patients to be able to respond to cues. When many parameters can be varied, a preclinical study could keep 1 that is readily manipulated as a constant, to help determine if it plays an important role in the task-related therapy.

Control Interventions

In drug trials, a placebo pill offers a reasonable comparison when a new class of medication is being tested. Unfortunately, pharmaceutical companies too often continue to test their new versions of an FDA-approved drug against a placebo, rather than against a medication approved for the same condition or in the same class. Their aim is to maximize the contrast in efficacy, which will get their version to market. It would be unfortunate if rehabilitation trials took this approach. Little will be learned that can be applied to patient care unless the latest intervention is compared to some form of active engagement of subjects. How much different ought the experimental intervention be from the control treatment?

One of the first comparisons for task-oriented training compared upper versus lower extremity training for task-specific outcomes for arm function and for walking.⁶ The positive if modest effects of specificity of training were shown. This control continues to be a design approach.⁴³

Although the EXCITE trial used an inactive control, it did include a crossover study at 1 year after entry, which will compare changes in the immediate versus delayed treatment groups. This feature may provide more insight into the longitudinal function of the patients and their responsiveness to CIMT at about 18 months after stroke, which could be construed as a type of control condition. The EXCITE investigators, however, made the somewhat misleading statement that about 50% of the control subjects received usual care and some community-based therapy after the intervention period (as did the experimental group), but that “their limited improvement in functional outcomes suggested that traditional neurorehabilitation interventions have limited effectiveness in promoting motor recovery.”² This comparison is an abrupt acceleration, because the so-called treatments included medications, splinting, general exercise, acupuncture, and other modalities of uncertain intention and duration that were not clearly geared to the function of the affected upper extremity.

A control intervention ought to be tailored to a likely need of the subjects and reach toward the focus of the primary outcome measure. The control condition should take into account the intensity of personal contact and attention, as well as the intensity of practice. It seems time to put a red light in front of designs that aim to prove the effects of specificity of training by, for example, using arm exercise as the control for an experimental walking therapy. The *what in compared to what* ought to be a vehicle that runs, rather than one with a dead battery. In the BACTRAC and robotic-assist trials, subjects who are not randomized to the experimental condition receive the same number of sessions of more conventional training of the affected upper extremity. The LEAPS control condition employs general exercise that may increase leg strength and balance, as well as equal contact, but no specific locomotor training for its walking-related outcomes. These vehicles are headed in the right direction.

Interim Measures

On a long drive, one needs landmarks to gauge progress. Several relevant interim measures during an intervention, as well as after it is completed, may offer insight into the effectiveness and dose of a therapy. The measures need not produce practice effects that alter the primary outcome measures.

In EXCITE, it would have been of great interest to know when the treated subjects changed their ability to perform the timed tasks on the Wolf Motor Function Test.⁴⁴ Did gains appear within a few days, 1 week or take the 2 full weeks of the intervention? If patients were still improving between 1 and 2 weeks, should the intervention have been stopped? Interim measures were employed at 4 and 8 months in EXCITE, but not during the treatment phase. In SCILT, key measures were collected every 2 weeks during the intervention. The analysis of these measures allowed assessment of the internal consistency of the results and offered insight into recovery of functional walking over time, which may help power future trials.⁵ In LEAPS, several outcomes are tested after intervals of training at 12, 24, and 36 sessions. These measures may demonstrate if and when the arms of the trial separate in gains and give further evidence for dose-response requirements.

Functional neuroimaging ought to inform rehabilitation studies beyond the behaviors we can measure.²⁶ The imaged action ought to be highly relevant to the target of the intervention and the targeted primary outcome measure. It is no longer enough simply to find a statistically significant change in a region of interest and a selected behavior between pretests and posttests. Serial scans during the time of the intervention may reveal patterns of activity and behavior that offer more solid insights into the brain-behavior effects of interventions.^{30,45,46}

Outcome Measures

Measurement tools with continuous outcomes are more likely to reflect gains than functional activity scales that do not employ ratio or interval measures.⁹ Occasional studies have suggested that continuous scaling outcomes such as walking speed or distance have an impact on walking-related performance during daily activities,⁴⁷ but these relationships are imperfect.⁴⁸ In addition, the goals of practice must be reflected in the outcome measures. Aside from the issue of reliability, sensitivity, and validity for the disease and disability being studied, the outcome measures must also determine whether the treatment has a high impact on the health-related quality of life of patients. For example, in EXCITE, the amount of use of the affected upper extremity may have significantly increased, but that increase may not be clinically robust if subjects still use the affected hand only half as much as usual. Also, the choice of control intervention may affect the outcome measure. For example, by choosing a self-evaluation scale of hand use, the EXCITE trial may have introduced a bias. The CIMT group may have had higher expectations for its self-appraisal, because it worked a lot of hours and received much more encouragement than the untreated control group. As a different sort of example, a study for walking that employs an upper extremity therapy as the control condition for patients, then trains them to stand and move about while they wash, cook, and carry items, could inadvertently improve walking ability.

A possible problem in SCILT and EXCITE was that the primary outcome measures for walking and functional use of the affected hand were closely aligned to what the active treatment group practiced during formal and informal therapy. That may make the efficacy measures more likely to reveal better outcomes, since to some degree subjects had practiced for the final examination. Both trials, however, tested continuous variables that were not specifically trained—walking speed and distance and timed upper extremity tasks—even though the tasks per se did not differ much from the repertoire of training tasks. LEAPS has chosen a dichotomous outcome by aiming to increase the walking speed of those who entered at a very slow and a moderately faster velocity to achieve, respectively, limited and unlimited community ambulation velocities. Continuous variables, dichotomized or not, may best serve as primary outcomes for the initial power analysis of a task-oriented MRCT. Functional scales that are closely aligned to improved speed, precision, strength, etc may best serve as secondary outcomes to relate the primary outcome to clinically important function and quality of life.

CONCLUSION

Now that the foot of the rehabilitation clinician is on the accelerator, trialists need to make sure that they do not drive recklessly. MRCTs are arduous, expensive, and provide very delayed, if any, gratification. To randomize vulnerable patients to an intervention that is not yet roadworthy is not ethical. Careful investigators will drive within the speed limit to destinations that must be reached, including the roads to dose-response curves and worthy interim and primary outcome measures, before setting out for the golden goal posts of the MRCT.

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Figure 1.

Time-dependent functional imaging and skills acquisition. Techniques such as functional magnetic resonance imaging (fMRI) assess the increase or decrease in synaptic activity in response to a stimulus such as finger tapping or word generation. This evoked response represents short-term (left column) spatiotemporal activity on a background of long-term (right column) adaptations in the strength of synapses that are involved in the action. Other techniques, such as positron emission tomography (PET), provide better insight into chronic or baseline states of metabolic activity, as well as acutely evoked changes in the intensity of the imaging signal compared to the resting state. This dynamic neural metabolism, then, is a moving target for assessment of the functional anatomy of the patient undergoing rehabilitation. It is possible, then, that a change in the evoked fMRI or transcranial magnetic stimulation (TMS) signal from preintervention to postintervention will not represent the effects of the therapy, the reacquisition of a skill, or a causal brain-behavior relationship. The interpretation of maps of functional anatomy and behavior would be strengthened if neural activity and behaviors were examined repeatedly with planned interim measures during the course of a therapy and as synaptic efficacy was being altered. The increased number of associations between maps and behavioral outcomes that were relevant to the training would provide insight into dose-response relationships and augment the face validity of their significance. NIRS = near-infrared spectroscopy; MEG =

magnetoencephalography; CBF = cerebral blood flow; CBV = cerebral blood volume; SPECT = single photon emission tomography.

Table 1

Enrichment strategies for multicenter randomized trials of a task-related intervention.

1	Consider the relevance and applicability to the human condition of laboratory-based research that employed preclinical animal models of a disease, impairment, and intervention.
2	Consider the reliability and applicability of observations made in pilot clinical studies performed on convenience samples with an evolving experimental methodology.
3	Preliminary studies ought to offer robust enough results to suggest at least a moderate effect size before they are submitted to an MRCT.
4	Define the essential elements of the intervention and their mechanisms of action.
5	Select the characteristics of the population most likely to respond to a treatment strategy: age, impairments, spared function, comorbidity, optimal time after injury, natural history of change over time, impact of lessening an impairment or disability, etc.
6	Consider anatomic, physiologic, functional neuroimaging, behavioral, genetic, and other potential biomarkers of efficacy to help guide entry criteria for subjects who are most likely to respond.
7	Determine the dose of task-specific rehabilitation to promote activity-dependent plasticity and the greatest change in the targeted behavior.
8	Use meaningful control conditions; early pilot studies may use a comparison against no intervention, but an MRCT ought to use an accepted practice-oriented comparison.
9	Perform pretrial studies that develop realistic estimations of the number of subjects needed to recruit and randomize (anticipated effect size) for a trial.
10	Use ratio or interval outcome measures, if feasible, that are sensitive to the spectrum of severity of impairment and disability to be encountered, as well as being sensitive to the likely change induced by the intervention. Use relevant scales of functioning and participation as allied outcomes of hypothesis-specific measures.
11	Minimize the variability of the assessment of outcomes across sites.
12	Consider adaptive methods for the treatment phase (dose escalation or incorporating subjects with increasingly greater levels of impairment) and for analysis of outcomes (interim measures, Bayesian algorithms).