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Rehabilitation and Functional Neuroimaging Dose-Response Trajectories for Clinical Trials

Bruce H. Dobkin

Background. In clinical trials, behavioral outcomes and physiological measures of activity-dependent plasticity that evolve with task-oriented therapies may fail to reach statistical significance. When significant, clinical effectiveness may not be robust enough to alter professional practices. Objective. Provide the conceptual basis for a research design to optimize the effect of an experimental treatment. Methods. Literature review. Results. Research designs usually do not take into consideration the dynamic state of each subject's potential responsiveness to an intervention. Providing a rational, rather than convenient, intensity and duration of therapy may remedy this potential confounder for clinical trials. To determine whether a most effective dose of a therapy exists, investigators could assess subjects before the intervention, administer interim measures at planned intervals, and continue the intervention until the primary behavioral outcomes or functional imaging parameters or both reach a plateau for at least 15 h of additional treatment. Conclusion. Promising interventions ought to be continued in phase II/III trials until subjects reach an asymptote in the primary outcome for behavioral gains. For neuroimaging studies that aim to correlate brain-behavior measures during rehabilitation, the specific intervention should also continue until behavioral gains and cerebral adaptations have attained a persistent plateau. Future trials can investigate whether functional neuroimaging performed in parallel with repeated behavioral assessments can better inform researchers about the optimal duration of an experimental therapy and a subject's maximal capacity for intervention-induced cerebral reorganization.

Key Words: Stroke—Motor learning—Plasticity—Physical therapy—fMRI—Transcranial magnetic stimulation.

Neurorehabilitation studies of interventions for motor and cognitive impairments or disabilities aim to determine whether a defined treatment improves an outcome that is relevant to the therapeutic strategy and of value to patients. Functional neuroimaging studies, such as transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI), have been employed in cross-sectional and longitudinal studies to assess for cerebral adaptations over time and, increasingly, over the course of a particular physical or cognitive therapy. Both types of studies almost always suffer from a confounder that makes their interpretation and their generalizability moot. Whether a within-subjects pre- and posttest design or an across-subjects group design, almost all publications to date have failed to determine the optimal dose of the intervention before instituting a larger trial. Many other facets of clinical rehabilitation trials¹ and rehabilitation imaging studies² need to be addressed, but strategies to find the most effective intensity and duration of training have received remarkably little attention.

Rehabilitation trials ought to account for the dynamic moving target referred to as neuroplasticity.³ Every prospective clinical intervention falls on an ongoing evolution of behavioral and neural adaptations. At any time after damage, the neural substrate may inhibit, leave in a basal state, or potentiate behavioral gains and neurophysiological maps of thoughts and movements. Dose-response interactions represent a challenge

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to clinical research methodology, especially for nonpharmacological interventions. The failure to develop models, however, that account for the physiological and behavioral continuum of experience-induced plasticity may limit the ability of clinicians to establish better treatments for neurological rehabilitation.

THE PROBLEM

Inasmuch as the physiology and microstructure of the nervous system continuously change under the myriad influences of the internal and external environment, how can the investigator design a study that locates the peak behavioral effects of training and the maximal modifications in brain circuitry that accompany training? How may an investigator control for the behavioral and physiological status of patients along their trajectory of potential gains after stroke, traumatic brain injury, or exacerbation of multiple sclerosis? If the treatment strategy being assessed has failed to alter the targeted behavior or neuroimaging parameter, could the intensity of the treatment have been inadequate? Perhaps a failed intervention would have had a statistically and clinically significant impact if the optimal dose, rather than the most convenient dose of therapy, had been employed. And for the future, if both a behavioral and an imaging variable change over the time of gains can this interaction offer clinical insight that would not otherwise have been available?

Clinical trials of rehabilitation interventions take place on a background of uncertainty about the neural state of responsiveness to a strategy at any given start time and for any given intensity of treatment. Researchers have little information about the neural milieu that they must manipulate to improve a deficient skill in patients. A lesion produces a cascade of effects over cerebral space and time on spared ensembles and distributed assemblies of cells and their synapses. For example, gene expression for neurotransmitters and trophic and inhibitory substances evolves after onset of injury.⁴ Neurotransmitters and neuromodulators that contribute to attention, learning, decision making, reward, responsiveness to cues from therapists, and other processes may not be normally regulated or available after brain injury. Other potential confounders of responsiveness include a subject's premorbid level of skills and cognition, medications that may affect neurotransmitter

actions, and the cumulative behavioral experiences, environmental influences, and physiological adaptations that followed the injury and evolved with prior attempts to regain function. Despite these problems, some rehabilitation trials for improving use of the affected hand, walking, language, and other disabilities have shown that when a threshold for the amount of task-oriented practice is exceeded, patients achieve gains. In a meta-analysis of augmented therapy time, a small but statistically significant summary effect size was found for greater intensity of a therapeutic exercise within the 1st 6 months after stroke.⁵ These improvements, however, have been interpreted by the rehabilitation community as less than clinically robust, so the results have not altered practices. To leap the hurdle from statistical inference into real-world clinical practice, promising treatments may have to be pushed with greater intensity.

What are the parameters of dosing? Unlike pharmacological studies, the dose or intensity of a physical or cognitive therapy is not readily encapsulated. The frequency of training sessions, the duration of a session, and the total number of sessions are usually predefined for a trial. The dose delivered to a subject must also take into account the attentional requirements of tasks, the number and variations of repetitions of practice of each component of a task within the session, the progression of effort and amount of error tolerated as the skill changes within and between sessions, the goal for number or type of successfully completed tasks, and how feedback will be provided and tapered.⁵

Dose-response interactions are no less important for brain mapping studies. Experience-induced gains for a skill have been related to synaptic plasticity and manifested by changes in the activation or strength of recruitment of neuronal representations; changes in involvement of non-contiguous parts of the network that come into play with new demands; tuning of neurons to particular sensorimotor requirements; task-related changes in cortico-cortical and, in the case of motor skills, corticomotoneuronal coherence in the molecular bases for altering synaptic strength and morphology such as long-term potentiation (LTP) and depression (LTD); and other dynamic factors. Although the fundamental mechanisms for a rehabilitation-induced brain map adaptation and behavioral skills are shared, plasticity at the level of neurons and synapses can occur in the presence or absence of a measurable change in skill. Many

factors have limited the ability of investigators to draw causal links between cerebral activations and functional changes that evolve with task-oriented training.⁶ For example, the frequently cited microstimulation studies by Nudo and colleagues within the hand region of monkeys following a 500 μ ischemic lesion have revealed prelesion to postlesion physiological adaptations among neural representations for the fingers and wrist that evolved only by training finger grasping skills. The studies have not shown a clear correlation between training-induced plasticity and behavioral gains, however.^{7,8} In these elegant experiments, it is possible that the behavioral assessments are insensitive to subtle differences in performance skills of the forepaw, or other regions of the brain experience adaptations that better reflect behavioral change, or future studies will have to correlate smaller increments of change in behavior and physiology until an asymptote of behavioral gains and cerebral adaptations are both reached.

The challenge for mapping in neurorehabilitation has been to define relationships between postinjury, therapy-induced brain activations, and relevant behavioral recovery or lack of improvement. Maps obtained in one study of hand recovery after stroke often differ from another.⁹ Some differences may be explained by the moving trajectory of behavioral and neural adaptations that have not yet reached an asymptote. If the duration of postinjury experience or the dose of a specific therapy for these subjects is decided by convenience, rather than as a managed variable, the investigator may forfeit the opportunity to follow the patient's trajectory to its maximal plateau of behavior and functional cerebral adaptation.

Short-term modulation of synaptic efficacy by practice^{10,11} may be a step that must precede long-term gains and brain map remodeling. Automaticity implies that the acquired motor skill requires little effort to control its performance once fully learned. Neural representations for a learned skill change as subjects practice to the level of automaticity. For example, extensive training of healthy subjects on a serial reaction time task was necessary before they reached automaticity and all the dose-dependent adaptations in cortical and striatal regions acquired incrementally during the course of practice were revealed.¹² Serial fMRI and behavioral motor assessments in longitudinal studies of patients from the onset of stroke reveal changing patterns of activation within bilateral primary motor cortex

and other components of the motor-cognitive network after cortical¹³ and subcortical infarcts.¹⁴ An overall trajectory of gains with experience and unspecified training were associated in these studies with regional increases and decreases in the fMRI signal over the time of better hand function. The impact of the type and intensity of rehabilitation training and the practice parameters that led to skills acquisition and map remodeling were not addressed. When the type and intensity of a strategy such as constraint-induced movement therapy are defined, the behavioral and physiological changes may vary considerably across studies.¹⁵⁻¹⁷ These differences may be attributed to variable neural sparing across subjects, adaptations in regions that are not usually examined by the technique, such as the premotor cortex rather than the primary motor cortex for TMS studies,^{18,19} and to changes that evolve more in proximal than in distal upper extremity motor control within the time course of the study.²⁰ The dose of time and experience may be the most critical factor in the outcomes of these trials. Investigators need to recognize the possible impact of the prior experience of each subject in using the paretic upper extremity before therapy began and of limiting treatment to 2 weeks in most constraint-induced movement therapy approaches. These constraints make it unlikely that each subject starts or ends at the same point on the dynamic trajectory of motor and neural adaptations.

Functional neuroimaging is not a surrogate for behavioral, sensorimotor, cognitive, or language outcomes. TMS, fMRI, positron emission tomography, and other techniques may, however, shed light on whether the expected networks can be engaged by an intervention.^{3,21,22} For example, an immediate reduction in the asymmetry of the motor-evoked potential between the unaffected and affected hemisphere in selected patients with chronic hemiplegia in response to a single therapy session for the upper extremity predicted long-term improvement with additional therapy for the arm and hand.²⁰ Serial studies over the trajectory of gains may also reveal whether representational adaptations have reached a plateau as the optimal intensity of a rehabilitation strategy is achieved.^{20,23} Locomotor training, for example, led to gains in walking speed in parallel to expansion and then focusing of fMRI representations for ankle dorsiflexion in several motor regions, but the pattern of change was rather unique for each subject at every 2-week measurement interval.²³ How, then, can the dose-response trajectory be managed

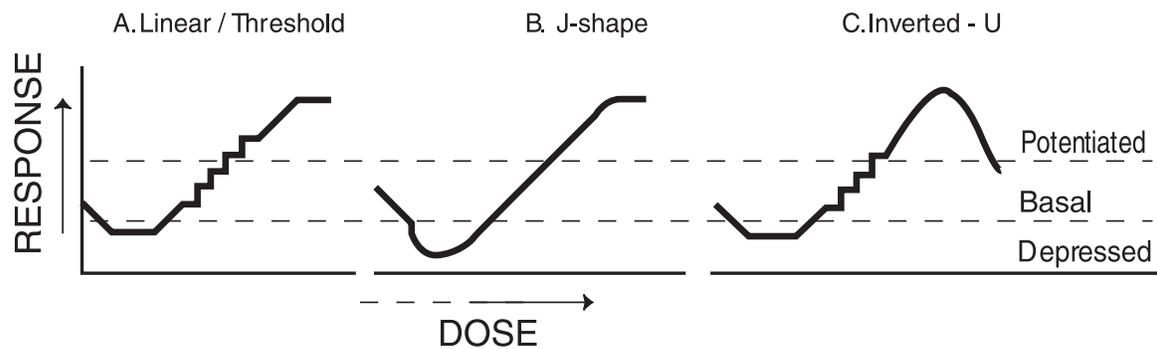


Figure 1. Dose-response trajectories for determining the optimal dose or duration of a rehabilitation intervention are shown as linear/threshold (A), J-shaped (B), and inverted-U (C) models. Repeated behavioral or physiologic brain mapping measures during the course of an open-ended pilot study will determine when the maximal benefit on behavior or full evolution of representational plasticity has reached a plateau.

so that the changes induced by a new rehabilitation strategy are as good as it gets?

THE SOLUTION

Examples of possible dose-response curves for rehabilitation interventions are shown in Figure 1. The *response axis* represents more skillful behavior, directional changes in physiological measures of learning such as LTP, and parameters relevant to functional cerebral anatomy that reflect task-specific learning (e.g., a higher motor-evoked potential or lower threshold using TMS; representational recruitment or focusing of activity by fMRI). These behavioral and physiologic responses do not, of course, go hand in hand. The *dose axis* is time after injury during which various experiences alter behavior and functional cerebral anatomy. This axis also includes the duration or levels of intensity of specific forms of practice. The horizontal dotted lines show possible physiologic states of the brain that may be encountered during normal learning, after injury, and during postinjury rehabilitation. The *basal state* represents the wide range of routine input-output computations of the brain. The *potentiated state* may be necessary for learning a skill. This state arises with repetitive practice or coherent inputs on neurons that lead to Hebbian plasticity, as well as drugs or electrical stimulation of peripheral nerves or the cortex that alter neuronal excitability and synaptic strengths. Potentiation may involve excitatory and inhibitory actions within neural assemblies and networks.

The subbasal, *depressed state* may follow an injury, although a rim of peri-infarct tissue soon after stroke may be highly plastic. A subbasal state may also reflect depletion of a neurotransmitter that affects the gain of signal-to-noise ratios during neuronal computations, poor attention while working at a task, and other factors that lessen the likelihood of learning and synaptic plasticity.

The exemplar trajectories in Figure 1 may behave as shifting fault lines under the pressure of subclinical events and computations. Clinical investigators cannot know where a subject falls along a skills acquisition curve, let alone which dose-response trajectory will best represent a subject. These brain states and curves are moving targets. In a *linear model* (Figure 1A), a response may be induced from the postinjury depressed state, then above the basal or control level in tandem with the dose of therapy, until no further gains are made. The dose of therapy may have to reach a threshold before more linear changes begin. Also, the rise will likely consist of small within- and between-session variations, not a steady or predictable change. A *J-shaped curve* (Figure 1B) might arise after an injury. The network to be engaged by training falls below the level of readiness. The subject, for example, may be in a hypometabolic state of diaschisis or may not have the attentional resources to learn. Training, perhaps along with stimulation by neurotransmitter precursors, may lead to gradual changes into a basal and finally a potentiated state. An *inverted-U response* (Figure 1C) is typical of many pharmacological agents. A higher dose may lead to a nega-

tive effect. That seems unlikely for a behavioral or cognitive therapy. Functional neuroimaging activations during the course of maximized behavioral learning, however, tend toward an inverted-U in regions that were initially active.^{12,23,24} In any model, the potentiated state and functional reorganization appreciated by fMRI or TMS may return toward the basal state even if the behavior remains skillful, because other related networks such as the basal ganglia come to more automatically store and subserve the behavior. Another interpretation of an inverted-U is that short-term unmasking of synapses leads to greater activation by fMRI and TMS, followed by long-term structural synaptic changes in both the cortical and subcortical portions of a distributed learning network.²⁵

To establish the optimal dose, a pilot study for a rehabilitation intervention might proceed as follows. The investigator makes pertinent decisions based on the conceptual basis for the experimental approach and the type of subjects to be studied, operationalizes the motor or cognitive rehabilitation goal, and defines the interventional strategy in as much detail as feasible, especially in terms of how to progress and reinforce training and how practice will proceed outside of formal training sessions. The primary outcome measure ought to reflect both the strategic focus of therapy and the goal of the intervention. For an fMRI study carried out at the same time, the investigator must define an activation paradigm during scanning that will incorporate an important component of the motor or cognitive skill being trained. To seek an optimal dose-response effect, the investigator could provide the intervention at 2 dosages along with a control intervention that prevents a Hawthorne effect. One dose may be highly practical, such as 3 times a week for 1-h sessions. The other dose may seem less practical but feasible, such as daily treatment 5 d a week for 2 h or 3 d a week for 3-h sessions. The aim is to randomly assign subjects to a substantial differential for treatment intensity, in this case by 3:1. Another approach could employ only 1 dose versus a control; if no statistically and clinically significant gains were found, the next experimental group would receive a higher dose by a factor of 3. The key design feature, however, goes beyond the weekly dose. Rather than fixing the duration of the trial, the investigator continues the intervention in a semi-open-ended fashion for all subjects, until the targeted behavior no longer improves in one group. For an imaging study, the duration is determined by when both the relevant

behavior and imaging variable cease to evolve. Both behavioral assessments and fMRI, TMS, or other physiological imaging could be used in tandem to determine when the evolution of both behavioral and adaptive changes reach a plateau, which may give the investigator mechanistic insight and greater certainty about having attained optimal gains with the intervention.

Given that a minimum of 16 h of additional therapy appeared to begin to differentiate outcomes in a meta-analysis of augmented therapy time,⁵ the dose-response aspect of a pilot study design ought to continue for at least an additional 2 weeks beyond an apparent plateau that has persisted for at least 2 weeks, or for 15 to 20 h of the intervention. A longer plateau of function may be needed for certain disabilities, such as a language or upper extremity skill compared to walking, before the trial can be concluded with confidence. Thus, subjects are trained until they reach an asymptote in an open-ended trial rather than for a fixed duration of the specified intensity of rehabilitation. Serial outcome measures are critical to this approach. One or more behavioral assessments will be necessary at baseline, after every 6 to 12 treatments, at the end of treatment, and at follow-up. At least 3 interim assessments, then, are likely to be needed. This schedule of assessments would also be employed for a functional imaging study of adaptations during rehabilitation. The differences in the effect size for the lower and higher doses of treatment, compared to the control intervention, will help determine whether to proceed to a phase III trial at 1 intensity and duration.

This approach to clinical research is similar to how clinicians practice. The dose and duration of a medication is increased, for example, until results are satisfactory or it is clear that the drug has no value or until adverse reactions and risks outweigh the benefits. As a rehabilitation study proceeds, it may become apparent that only a certain type of subject can benefit, such as the patient who has a less severe impairment.²⁶ This adaptive design conforms to a Bayesian approach to clinical trials as well.²⁷ The researcher accrues information during a pilot study and uses this information to alter aspects of the study's design, not unlike performing an interim futility analysis during a randomized clinical trial. Another advantage of serial measures arises from the inevitable loss of subjects or data points in clinical trials. A design with only pre- and postintervention measures eliminates that subject from all analyses. By scheduling serial observa-

tions during the course of an intervention, the loss of 1 assessment point still allows statistical approaches using, for example, the last observation carried forward. In addition, the baseline measure, such as the ability to elicit a motor evoked potential by TMS, may not be obtainable, but subsequent data collections over the trajectory of training may elicit physiological responses.²⁰ This brain-behavior relationship is precisely the sort that rehabilitation therapy studies would not want to miss. Indeed, this approach using functional imaging techniques may reveal incremental neural adaptations associated with behavioral gains over the time of treatment that allow for a stronger link of causality between brain mapping adaptations and behavior.

The burden on subjects and budgets may be greater in an open-ended, serial assessment design compared with trials with a preplanned duration and only pre- and posttesting. The effort contributed by each subject to the open-ended design, however, is more likely to provide reliable answers about the possible utility of a particular intervention. Indeed, it may be most ethical to use a somewhat more burdensome study design like this one than a protocol that is either too brief or longer than necessary to determine if a robust effect of training can be elicited.

CONCLUSIONS

Neural plasticity is modulated by experience and practice. To determine whether a rehabilitation intervention optimizes behavioral outcomes and physiologic adaptations, the investigator must provide the most productive dose of therapy. Phase II/III clinical trials should not be undertaken without including a design that seeks out the maximal dose-response curve for that intervention. Researchers who assess the functional reorganization induced by skills practice and learning paradigms should also consider dose-response procedures to determine whether they are capturing the full evolution of neural adaptations. High- versus lower-intensity task-oriented rehabilitation designs, accompanied by interim behavioral and functional neuroimaging measurements throughout a trial that has no prefixed duration, are one approach. These designs may prevent sound treatments from being dismissed because the investigator underplayed the trajectory of gains. They may increase the clinical robustness of treatments that achieve statistical significance so that

the experimental intervention gains acceptance as an evidence-based practice.

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