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Consideration of dose and timing when applying interventions after stroke and spinal cord injury

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Abstract

Nearly four decades of investigation into the plasticity of the nervous system suggest that both timing and dose could matter. This paper provides a synopsis of our lectures at the IV STEP meeting which presented a perspective of current data on the issues of timing and dose for adult stroke and spinal cord injury motor rehabilitation. For stroke, the prevailing evidence suggests that greater amounts of therapy do not result in better outcomes for upper extremity interventions, regardless of timing. Whether or not greater amounts of therapy result in better outcomes for lower extremity and mobility interventions needs to be explicitly tested. For spinal cord injury, there is a complex interaction of timing post injury, task-specificity, and the microenvironment of the spinal cord. Inflammation appears to be a key determinant of whether or not an intervention will be beneficial or maladaptive, and specific re-training of eccentric control during gait may be necessary. To move beyond the limitations of our current interventions and to effectively reach nonresponders, greater precision in task-specific interventions that are well-timed to the cellular environment may hold the key. Neurorehabilitation that ameliorates persistent deficits, attains greater recovery and reclaims non-responders will decrease institutionalization, improve quality of life and prevent multiple secondary complications common after stroke and SCI.

INTRODUCTION

Nearly four decades of investigation into the plasticity of the nervous system suggest that both timing and dose could matter. With respect to timing, a period of heightened neuroplastic responsiveness exists immediately after the central nervous system injury and may last one to three months post stroke^{1,2} and two years or more after spinal cord injury (SCI).³ With respect to dose, most rehabilitation studies have quantified the delivered intervention using the surrogate variable of time scheduled for therapy, which ignores important parameters, such as the amount of the active ingredient, its mechanism of action (including pathways and therapeutic target), and half-life.⁴ This paper provides a synopsis of

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our lectures at the IV STEP meeting which presented a perspective of current data on the issues of timing and dose for adult stroke and spinal cord injury motor rehabilitation. We have also operationally defined a few common terms in the hope of facilitating communication, science, and clinical practice (Box).

STROKE

A 2014 meta-analysis examined the importance of dose from a broad perspective.⁵ This meta-analysis included all motor stroke rehabilitation randomized, controlled trials that compared a higher dose of therapy with a lower dose of therapy, regardless of the interventions delivered. Included studies were not explicitly designed to address the question of dose, and therefore tested a variety of interventions at a variety of times post stroke. Time scheduled for therapy (cumulative hours over the duration of the intervention) was used as a surrogate variable of dose, because that was the only measure that could be consistently extracted from published trials, and outcomes were measured at the functional capacity level. Studies included were from all time points post stroke, with a greater proportion of published trials studying participants who were beyond 3 months post stroke. The result of the meta-analysis indicated that dose had a Hedges *g* effect size of ~0.35, indicating that more time scheduled for therapy had a modest, beneficial effect on functional capacity. Thus, when looking broadly across data from a collection of studies, more therapy appears to be better for people with stroke.

We recently completed an explicit test of the effect of dose.⁶ The goal was to examine how a range of doses of upper extremity movement practice affected functional outcomes in people with long-standing mild-to-moderate paresis post stroke, using a parallel, dose-response, randomized, controlled trial design (*n* = 85). The aims were to: 1) test whether larger total doses result in better outcomes than smaller total doses; and 2) characterize modifiers of the dose-response relationship. The key active ingredient of the intervention was task-specific actions of the upper limb, based on animal studies of plasticity. The task-specific intervention was adapted from rodent and non-human primate studies.⁷⁻¹³ Key adaptations for humans were: 1) having the goal of improved performance on a multitude of upper limb functions important for daily life, not just the goal of improving on a single, practiced task; 2) providing training on multiple functional tasks, not just one; 3) facilitating engagement by individualizing the tasks per participant preferences; and 4) not food-depriving the participants. Training included both unilateral and bilateral tasks, since both are necessary for upper limb function. In brief, the training was individualized to participant interests, graded to challenge motor capabilities and progress over time according to a standard protocol; extensive details and rationale for the intervention are available in a manual for clinicians¹⁴). Dose was quantified by number of repetitions of training. The four groups were total doses of 3600, 6400, 9600, and individualized maximum repetitions (see⁶ for details). The primary trial outcome was the slope of the Action Research Arm Test (ARAT, a measure of upper limb functional capacity) over the course of the intervention, which was delivered in four sessions per week for eight weeks for three dose groups and continued beyond 8 weeks for the individualized maximum group until performance plateaued.

Overall, there were improvements (Figure 1), with average ARAT gains of 5-8 points across the four groups, but no clear difference in response based on treatment dosage with slopes less than 1 point/week (for full details, see⁶). The magnitude of change seen here was similar to the magnitudes of change seen in many other motor rehabilitation studies at this later time point post stroke (for examples from recent studies see ¹⁵⁻¹⁷) and to changes in routine outpatient care,¹⁸ but is smaller than magnitudes of change seen earlier after stroke,^{19,20} when the natural trajectory of recovery exerts a powerful beneficial effect. Modest changes were also seen with the secondary outcomes of self-reported performance measured with the Stroke Impact Scale – Hand Function subscale and the Canadian Occupational Performance Measure. A full 90% of the participants perceived a meaningful improvement in their upper limb, but perceptions were not related to measured changes in capacity.⁶ Initial motor capacity, neglect, and seven other tested characteristics did not modify the dose-response relationship (see bottom half of Table 3 in ⁶).

Over the course of the trial, we developed novel metrics for capturing upper limb performance in daily life from accelerometer recordings.²¹⁻²⁵ Daily performance, i.e. what a person actually does in an unstructured environment, is distinguished from functional capacity, i.e. what a person is capable of doing in the structured environment of a clinic or laboratory.²⁶ Accelerometry metrics are responsive to change²⁷ and provide critical information about what a person actually does in daily life. One of the striking features from our neurologically-intact adults sample (n = 74) was the strong consistency across individuals in their daily upper limb performance as revealed from accelerometry profiles (see Figure 2 for representative examples). The intensity of activity (y-axis, Bilateral Magnitude) and the contribution of each limb (x-axis, Magnitude Ratio; zero indicating that both limbs contribute the same amount) are calculated for every second of data during 24+ hour wearing periods. The two bars on either side show the amount of isolated dominant and non-dominant limb use. The shape in the middle shows the large amount of time when the two limbs are used together. The plots are symmetrical, indicating that, contrary to expectations, the dominant and non-dominant upper limbs are used about the same amount of time and mostly together. The profiles are wider on the bottom, indicating that most upper limb movements are low intensity. The ‘rims’ of the bowl-like shape occur during activities where one limb is accelerating while the other is relatively still, such as placing objects in a container with one hand and holding the container with the other.²⁵ The ‘warm glow’ in the middle occurs during lower intensity movements where both limbs are working together, such as cutting food with a knife and fork.²⁵ The top peak occurs with higher intensity movements involving both limbs, such as stacking boxes on a shelf.²⁵ Despite the difference in activity level, the plots are remarkably consistent in shape and symmetry. This consistency held across all neurologically-intact adults. The highly constant features of upper limb performance in daily life make these profiles and their resulting metrics ideal for distinguishing typical from atypical performance and for assessing change in daily upper limb performance, which was done in the dose-response trial.

Despite progression of task difficulty during training (an indicator of learning) and changes in functional capacity over the course of the trial, there was no evidence of change in performance in daily life, as quantified by six different accelerometry metrics, either at the group or individual level.²⁸ The six metrics are indices of unilateral and bilateral activity,

quantifying intensity, magnitude, contributions from each limb, and variability throughout the day.²⁸ The lack of change in performance occurred in spite of formal bi-weekly and informal, per-session discussions with each participant about how they might incorporate use of the hand and arm into daily activities. Figure 3 shows group data from one metric, the activity (or use) ratio. This simple metric is the ratio of hours of use of one side compared to the other and is highly consistent in neurologically intact adults. Across the four groups, changes over time (slopes) are not different from zero and the values do not approach normal (gray shaded area). Examination of slopes of all 6 metrics for every individual also failed to find evidence of positive change in anyone. Even in those who made the largest changes in capacity, there were no changes in performance in daily life, as can be seen in the accelerometry profiles from one representative individual with an 18 point improvement on the ARAT (Figure 4).

Conclusions for stroke thus far

The trial was a strong, explicit test of the effect of dose on outcomes. Larger amounts of therapy were not better at 6 months or more post stroke, as evidenced by small improvements in functional capacity (< 1 point changes/week), no consistent dose-response relationship, and the fact that none of the variables modified the dose-response relationship. We question the relevance of the changes in functional capacity, since self-perception of improvement was not related to measured improvement in functional capacity and no one changed their performance at home in daily life. From these trial results, we must conclude that intensive, progressive, task-specific training is not worth the effort for people with mild-to-moderate upper limb paresis at or beyond 6 months post stroke.

Because this was a single trial, we consider these results in the context of a few larger stroke rehabilitation trials and their implications for clinical practice. The one other upper limb dose-response trial also failed to find a dose response effect.²⁹ That trial was early after stroke, enrolling people with moderate-to-severe upper limb paresis within 8-84 days post stroke. The 2015 ICARE trial was not designed as a dose-response trial, testing the Acquired Skills Acquisition Program compared to a dose-matched group receiving usual care and a group receiving usual and care that was not dose-matched.³⁰ Their results showed large changes in upper limb functional capacity for people with upper limb paresis 14-106 days after stroke in all three groups, regardless of dose or intervention.²⁰ Thus, large improvements can occur early after stroke, i.e. 'natural recovery', that therapy may be able to guide toward improved capacity and performance in daily life. Specific interventions currently in use and the amount of therapy provided likely have minimal effect on overall upper limb outcomes. Later after stroke, the best approach may be to focus on adaptive equipment and/or compensatory approaches for the affected upper limb in a short episode of care, which hopefully can directly facilitate performance in daily life.

In contrast to upper limb trials, there is still the possibility that more may be better for mobility interventions any time after stroke. The LEAPS trial resulted in large changes in walking ability with larger amounts of therapy, regardless of time or intervention.³¹ Importantly, improved mobility was seen in both functional capacity and daily performance outcomes. Likewise, the smaller VIEWS trial indicated that greater amounts and

cardiovascular-intensive training produce better mobility.³² There has not yet been an explicit test of dose on stroke mobility outcomes; a well-designed study to address this issue is sorely needed.

SPINAL CORD INJURY

Task-specific training for individuals with SCI represented a paradigm shift in rehabilitation in order to promote functional gains, and improve health and quality of life.³³ One type of activity-based rehabilitation uses manual assistance and treadmill training. In a large study (n=225), using a pre-post design, this type of locomotor training produced significant gains in strength and community ambulation in people with incomplete tetra- or paraplegia (AIS C&D).³ Unfortunately, intensive training was not equally effective across patients, with 22% non-responders that did not regain ambulation. New, more specific neurorehabilitation interventions will be required to promote recovery in even the toughest cases.

Promoting recovery is a complex, multidimensional interaction, which we have reduced to three domains to begin with – *Intervention Timing* early or late after SCI, *SCI Mechanisms* at the injury site and remote regions, *Task Specific Rehabilitation*. Further, we use rodent SCI models in which lesion heterogeneity can be controlled experimentally. Mid-thoracic, computer-controlled contusion in rodents is reproducible, can be graded, and replicates human SCI.^{34,35} Indeed, the neuropathology and inflammatory cascade in mice and rats align closely to the few studies available in human SCI.³⁶ Here we focus on mid-thoracic SCI and the consequences of this injury on regions very far from the primary injury, like the lumbar cord. Neuro-inflammation is an early, lesion magnifier that also creates neuropathic pain-like conditions below the injury.³⁷⁻³⁹ The neuromodulatory effects of inflammation on motor systems and locomotor recovery is unknown.

An early mediator of inflammation is the extracellular matrix degradation enzyme, matrix metalloproteinase 9 (MMP-9). In human SCI, MMP-9 is elevated at the injury site, supporting the need for studies in experimental SCI.⁴⁰ This proteinase activates inflammatory cytokines and chemokines within the cord to produce an inflammatory microenvironment quite far from the injury site in the lumbar cord surrounding the central pattern generators of locomotion (CPGs).⁴¹ The impact of inflammation on rehabilitation, specifically treadmill training, was studied for the first time using a murine contusion model in which MMP9 was genetically eliminated [MMP9 knock out (KO)] to block inflammation. Genetically-normal mice (called wild-type mice) have pronounced inflammation early after SCI and served as controls. Treadmill-based rehabilitation occurred 2-9 days after SCI with long-term follow-up 1 month after training ended. Robust locomotor recovery occurred only when treadmill training was delivered without inflammation (ie MMP9 KO; Figure 5).⁴¹ However, the same training delivered when inflammation was high (wild type) produced lasting locomotor deficits (Figure 5). These deficits were greater than had no treadmill training been administered. Delivering the same training late after SCI, days 35-42, when inflammation had resolved, had no effect in MMP-9 KO or wild-type groups,⁴¹ suggesting that there is an important window for rehabilitation early but not late after injury. However, treadmill training delivered early is harmful if inflammation is not blocked. Effective

rehabilitation depends on more than the type or timing of the intervention; the inflammatory microenvironment is critical.

Identifying the source of inflammation within the spinal cord is important if we are to develop treatments to control inflammation during rehabilitation. Given that MMP-9 is localized around vasculature in the lumbar microenvironment after mid-thoracic SCI, it could potentially be degrading the endothelial junctions and allowing peripheral white blood cells from the bone marrow, specifically neutrophils and monocytes, through the blood brain barrier into “protected regions” away from the SCI. In this way, these cells could cause inflammation. Using bone marrow transplantation techniques in mice, we added a green fluorescent tag to bone-marrow cells to distinguish them from inflammatory cells residing in the cord. Within 24 hrs of SCI, green bone-marrow cells appeared in the lumbar cord, 10-12 segments below the injury (Figure 6).⁴² Surprisingly, peripheral cells did not invade the cervical cord above the injury which indicates that this is a localized rather than general response after SCI.⁴² These infiltrating bone-marrow cells have higher inflammatory profiles than resident cord cells and early treadmill training (2-9 days) primes these invading cells to even higher inflammatory toxic profiles (Figure 7).⁴³ Thus, the primary source of early, harmful inflammation are bone marrow-derived cells and early rehabilitation worsens inflammation. It is also clear that the remote lumbar cord is part of the “injury site” rather than being relatively protected. Peripheral inflammatory sources may allow easier, more effective anti-inflammatory treatment of the cord.

The effects of the inflammatory microenvironment on structural neuroplasticity, learning and reflexes are unknown. Given the toxic profile of the lumbar cord, maladaptive plasticity must be considered across lesion severities and over time. Lumbar interneurons within known central pattern generator (CPG) locations were examined in rats with either moderate contusion SCI or complete cord transection, the most severe form of injury and most stringent control for inflammation. Early after injury, interneuron atrophy and abnormal synaptic formations were evident, with greater abnormalities occurring as severity increased.⁴⁴ Electrophysiological testing of the ankle dorsiflexor reflex showed marked hyperexcitability regardless of severity of SCI.⁴⁴ The test for segmental learning required the rat to learn to hold the paw above a saline solution to avoid a small shock to the tibialis anterior (TA). Shock was delivered when the leg muscles relaxed and a metal rod attached to the paw contacted the solution, closed a circuit and delivered a shock. This segmental learning paradigm is well established and can distinguish adaptive from maladaptive plasticity within the lumbar cord.⁴⁵⁻⁴⁷ Normal segmental learning in this paradigm is typified by spending ~40s of each minute out of the water over 30 minutes. Early after injury when lumbar inflammation is the highest, segmental learning is lost across lesion severities – the paw is submerged most of the time. Thus, high inflammation early after moderate or complete SCI contributes to maladaptive changes in structural plasticity, hyperreflexia and loss of segmental learning in the lumbar cord.⁴⁴ Interestingly, these maladaptive changes worsen over time (35d), except segmental learning with incomplete SCI. Late after injury, when inflammation has resolved, some segmental learning emerges and the paw is held above the water for intermediate periods (~ 30s/min), suggesting that not all maladaptive changes are permanent. Some learning substrates, like synaptic structures and function, appear to be available in the lumbar cord for locomotor rehabilitation later.⁴⁴

Despite evidence of a capacity for lumbar segmental learning late after contusion, clearly treadmill training was ineffective even when the MMP-9 inflammatory pathway was blocked throughout the course of SCI. At least one explanation of these contradictory findings is that rehabilitation may need to be even more task specific to take advantage of these segmental learning substrates late after SCI. By using rehabilitation approaches that specifically target persistent deficits, will it be possible to lengthen the window for adaptive plasticity and improve recovery beyond current approaches?

The loss of eccentric motor control may be the most resistant impairment to rehabilitation. Eccentric control requires a precise gradation of descending drive from the brain to match peripheral muscle actions amongst a changing, dynamic environment. Not surprisingly, eccentric skill acquisition occurs late in development and is impaired in most neurological conditions. If precise matching is lost, serious functional deficits occur. If brain input exceeds muscle afferent activity, the muscles isometrically contract and the limb is used as a strut. If the brain drive is low, the muscles fail eccentrically and the limb collapses. Because these eccentric deficits occur after intensive, activity-based locomotor training in both humans and rodents, a task-specific, eccentric training program may have greater benefits. In a strong proof-of-principle design, we delivered eccentrically-demanding downhill assisted treadmill training late after SCI when flat treadmill training had failed. Eccentric training restored joint coordination and fractionated movements while traditional flat training failed (Figure 8). Specific kinematic elements also showed significant robust recovery with eccentric but not flat treadmill training including near normal toe clearance and dynamic trunk control during locomotion (Figure 8). Furthermore, eccentric training capitalized on learning substrates to induce normal segmental learning late after SCI which correlated with greater ankle control and toe clearance during walking. Lastly, eccentric training reduced lumbar inflammatory cytokines which are slightly elevated by flat treadmill training. Thus, eccentric treadmill training induces important functional gains and improves the lumbar microenvironment, both of which were unattainable with flat training.

Conclusions for SCI thus far

These series of experiments illustrate the complexity in identifying the optimal treatment window and the best form of treatment to restore function after SCI. A multidimensional approach is required to understand the beneficial and detrimental interactions over time and a single type of activity-based rehabilitation is unlikely to be uniformly effective. Rather, precisely-targeted, task-specific eccentric rehabilitation that is timed to coincide with the most permissive microenvironment is especially effective in experimental SCI and is currently being tested in chronic incomplete SCI in humans. Importantly, a poor outcome doesn't mean the intervention is bad. For patients that fail to respond to rehabilitation, we must ask ourselves: is the intervention task-specific enough? Is an otherwise beneficial treatment being blocked by cellular factors like inflammation? Have we waited too long to deliver the training and the window for natural repair and plasticity has closed? Recently, we translated eccentric treadmill training from rodents to human SCI and are testing whether overground locomotion, strength and quality of life improve. Completion of these studies will optimize when and how to deliver rehabilitation for individuals with SCI.

CONCLUSIONS

While accumulated knowledge has translated into improved interventions for neurorehabilitation (e.g. constraint-induced movement therapy, intensive gait training), most research and clinical interventions lead to minimal improvements in neural impairments beyond what might be expected from natural recovery, along with much larger improvements in the functional abilities. In other words, motor rehabilitation teaches people to do what needs to be done in daily life with the spared neural substrate available. To move beyond these limitations and to effectively reach non-responders, greater precision in task-specific interventions that are well-timed to the cellular environment may hold the key. Knowing that neuroinflammation can be a barrier to functional recovery, conditions such as stroke and traumatic brain injury might also be impacted. Neurorehabilitation that ameliorates persistent deficits, attains greater recovery and reclaims non-responders will decrease institutionalization improve quality of life and prevent multiple secondary complications common after stroke and SCI.

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REFERENCES

1. Overman JJ, Carmichael ST. Plasticity in the injured brain: more than molecules matter. *Neuroscientist*. Feb; 2014 20(1):15–28. [PubMed: 23757300]
2. Nudo RJ. Recovery after brain injury: mechanisms and principles. *Frontiers in human neuroscience*. 2013; 7:887. [PubMed: 24399951]
3. Buehner JJ, Forrest GF, Schmidt-Read M, White S, Tansey K, Basso DM. Relationship between ASIA examination and functional outcomes in the NeuroRecovery Network Locomotor Training Program. *Archives of physical medicine and rehabilitation*. Sep; 2012 93(9):1530–1540. [PubMed: 22920450]
4. Lang CE, Lohse KR, Birkenmeier RL. Dose and timing in neurorehabilitation: prescribing motor therapy after stroke. *Current opinion in neurology*. Sep 19.2015
5. Lohse KR, Lang CE, Boyd LA. Is more better? Using metadata to explore dose-response relationships in stroke rehabilitation. *Stroke; a journal of cerebral circulation*. Jul; 2014 45(7):2053–2058.
6. Lang CE, Strube MJ, Bland MD, et al. Dose-response of task-specific upper limb training in people at least 6 months post stroke: A Phase II, single-blind, randomized, controlled trial. *Annals of Neurology*. in press.
7. Barbay S, Plautz EJ, Friel KM, et al. Behavioral and neurophysiological effects of delayed training following a small ischemic infarct in primary motor cortex of squirrel monkeys. *Exp Brain Res*. Feb; 2006 169(1):106–116. [PubMed: 16273404]
8. Friel KM, Heddings AA, Nudo RJ. Effects of postlesion experience on behavioral recovery and neurophysiologic reorganization after cortical injury in primates. *Neurorehabilitation and neural repair*. 2000; 14(3):187–198. [PubMed: 11272475]
9. Kleim JA, Barbay S, Nudo RJ. Functional reorganization of the rat motor cortex following motor skill learning. *J Neurophysiol*. Dec; 1998 80(6):3321–3325. [PubMed: 9862925]
10. Nudo RJ, Milliken GW. Reorganization of movement representations in primary motor cortex following focal ischemic infarcts in adult squirrel monkeys. *J Neurophysiol*. May; 1996 75(5): 2144–2149. [PubMed: 8734610]

11. Nudo RJ, Milliken GW, Jenkins WM, Merzenich MM. Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. Jan 15; 1996 16(2):785–807. [PubMed: 8551360]
12. MacDonald E, Van der Lee H, Pocock D, et al. A novel phosphodiesterase type 4 inhibitor, HT-0712, enhances rehabilitation-dependent motor recovery and cortical reorganization after focal cortical ischemia. *Neurorehabilitation and neural repair*. Nov-Dec;2007 21(6):486–496. [PubMed: 17823313]
13. Remple MS, Bruneau RM, VandenBerg PM, Goertzen C, Kleim JA. Sensitivity of cortical movement representations to motor experience: evidence that skill learning but not strength training induces cortical reorganization. *Behav Brain Res*. Sep 14; 2001 123(2):133–141. [PubMed: 11399326]
14. Lang, CE., Birkenmeier, RL. *Upper-Extremity Task-Specific Training after Stroke or Disability: A Manual for Occupational Therapy and Physical Therapy*. 1 ed.. AOTA Press, Inc.; Alexandria, VA: 2013.
15. Ackerley SJ, Byblow WD, Barber PA, MacDonald H, McIntyre-Robinson A, Stinear CM. Primed Physical Therapy Enhances Recovery of Upper Limb Function in Chronic Stroke Patients. *Neurorehabilitation and neural repair*. Jul 15;2015
16. Young BM, Nigogosyan Z, Walton LM, et al. Dose-response relationships using brain-computer interface technology impact stroke rehabilitation. *Frontiers in human neuroscience*. 2015; 9:361. [PubMed: 26157378]
17. Wolf SL, Sahu K, Bay RC, et al. The HAAPI (Home Arm Assistance Progression Initiative) Trial: A Novel Robotics Delivery Approach in Stroke Rehabilitation. *Neurorehabilitation and neural repair*. Nov; 2015 29(10):958–968. [PubMed: 25782693]
18. Lohse K, Bland MD, Lang CE. Quantifying change during outpatient stroke rehabilitation: A retrospective regression analysis. *Archives of physical medicine and rehabilitation*. Apr 21;2016
19. Dromerick AW, Lang CE, Birkenmeier RL, et al. Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS): A single-center RCT. *Neurology*. Jul 21; 2009 73(3):195–201. [PubMed: 19458319]
20. Winstein CJ, Wolf SL, Dromerick AW, et al. Effect of a Task-Oriented Rehabilitation Program on Upper Extremity Recovery Following Motor Stroke: The ICARE Randomized Clinical Trial. *Jama*. Feb 9; 2016 315(6):571–581. [PubMed: 26864411]
21. Bailey RR, Lang CE. Upper-limb activity in adults: referent values using accelerometry. *J Rehabil Res Dev*. 2013; 50(9):1213–1222. [PubMed: 24458962]
22. Bailey RR, Birkenmeier RL, Lang CE. Real-world affected upper limb activity in chronic stroke: an examination of potential modifying factors. *Topics in stroke rehabilitation*. Feb; 2015 22(1):26–33. [PubMed: 25776118]
23. Bailey RR, Klaesner JW, Lang CE. Quantifying Real-World Upper-Limb Activity in Nondisabled Adults and Adults With Chronic Stroke. *Neurorehabilitation and neural repair*. Nov-Dec;2015 29(10):969–978. [PubMed: 25896988]
24. Urbin MA, Bailey RR, Lang CE. Validity of body-worn sensor acceleration metrics to index upper extremity function in hemiparetic stroke. *Journal of neurologic physical therapy : JNPT*. Apr; 2015 39(2):111–118. [PubMed: 25742378]
25. Bailey RR, Klaesner JW, Lang CE. An accelerometry-based methodology for assessment of real-world bilateral upper extremity activity. *PloS one*. 2014; 9(7):e103135. [PubMed: 25068258]
26. WHO. *Towards a common language for Functioning, Disability, and Health: ICF*. World Health Organization; Geneva: 2002.
27. Urbin MA, Waddell KJ, Lang CE. Acceleration Metrics Are Responsive to Change in Upper Extremity Function of Stroke Survivors. *Archives of physical medicine and rehabilitation*. Dec 9;2014
28. Waddell KJ, Strube MJ, Bailey RR, et al. Does task-specific training improve upper limb performance in daily life post-stroke?. In Review.

29. Hunter SM, Hammett L, Ball S, et al. Dose-response study of mobilisation and tactile stimulation therapy for the upper extremity early after stroke: a phase I trial. *Neurorehabilitation and neural repair*. May; 2011 25(4):314–322. [PubMed: 21282528]
30. Winstein CJ, Wolf SL, Dromerick AW, et al. Interdisciplinary Comprehensive Arm Rehabilitation Evaluation (ICARE): a randomized controlled trial protocol. *BMC neurology*. 2013; 13:5. [PubMed: 23311856]
31. Duncan PW, Sullivan KJ, Behrman AL, et al. Body-weight-supported treadmill rehabilitation after stroke. *N Engl J Med*. May 26; 2011 364(21):2026–2036. [PubMed: 21612471]
32. Holleran CL, Straube DD, Kinnaird CR, Leddy AL, Hornby TG. Feasibility and potential efficacy of high-intensity stepping training in variable contexts in subacute and chronic stroke. *Neurorehabilitation and neural repair*. Sep; 2014 28(7):643–651. [PubMed: 24515925]
33. Behrman AL, Bowden MG, Nair PM. Neuroplasticity after spinal cord injury and training: an emerging paradigm shift in rehabilitation and walking recovery. *Physical therapy*. Oct; 2006 86(10):1406–1425. [PubMed: 17012645]
34. Jakeman LB, Guan Z, Wei P, et al. Traumatic spinal cord injury produced by controlled contusion in mouse. *Journal of neurotrauma*. Apr; 2000 17(4):299–319. [PubMed: 10776914]
35. Bunge, RP. Clinical implications of recent advances in neurotrauma research.. In: Salzman, SK., Faden, AI., editors. *The neurobiology of central nervous system trauma*. Oxford University Press; New York NY: 1994. p. 329-339.
36. Bunge RP, Puckett WR, Becerra JL, Marcillo A, Quencer RM. Observations on the pathology of human spinal cord injury. A review and classification of 22 new cases with details from a case of chronic cord compression with extensive focal demyelination. *Advances in neurology*. 1993; 59:75–89. [PubMed: 8420126]
37. Detloff MR, Fisher LC, McGaughy V, Longbrake EE, Popovich PG, Basso DM. Remote activation of microglia and pro-inflammatory cytokines predict the onset and severity of below-level neuropathic pain after spinal cord injury in rats. *Experimental neurology*. Aug; 2008 212(2):337–347. [PubMed: 18511041]
38. Gwak YS, Hulsebosch CE. Remote astrocytic and microglial activation modulates neuronal hyperexcitability and below-level neuropathic pain after spinal injury in rat. *Neuroscience*. Jul 7; 2009 161(3):895–903. [PubMed: 19332108]
39. Hains BC, Waxman SG. Activated microglia contribute to the maintenance of chronic pain after spinal cord injury. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. Apr 19; 2006 26(16):4308–4317. [PubMed: 16624951]
40. Buss A, Pech K, Kakulas BA, et al. Matrix metalloproteinases and their inhibitors in human traumatic spinal cord injury. *BMC neurology*. 2007; 7:17. [PubMed: 17594482]
41. Hansen CN, Fisher LC, Deibert RJ, et al. Elevated MMP-9 in the lumbar cord early after thoracic spinal cord injury impedes motor relearning in mice. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. Aug 7; 2013 33(32):13101–13111. [PubMed: 23926264]
42. Hansen CN, Norden DM, Faw TD, et al. Lumbar Myeloid Cell Trafficking into Locomotor Networks after Thoracic Spinal Cord Injury. *Experimental neurology*. Aug.2016 282:86–98. [PubMed: 27191729]
43. Norden DM, Faw TD, McKim D, et al. Infiltration of macrophages promotes inflammation rapidly at epicenter and remote regions after thoracic SCI. *Journal of neurotrauma*. 2016; 33:A50.
44. Hansen CN, Faw TD, White S, Buford JA, Grau JW, Basso DM. Sparing of Descending Axons Rescues Interneuron Plasticity in the Lumbar Cord to Allow Adaptive Learning After Thoracic Spinal Cord Injury. *Frontiers in neural circuits*. 2016; 10:11. [PubMed: 26973469]
45. Grau JW, Crown ED, Ferguson AR, Washburn SN, Hook MA, Miranda RC. Instrumental learning within the spinal cord: underlying mechanisms and implications for recovery after injury. *Behavioral and cognitive neuroscience reviews*. Dec; 2006 5(4):191–239. [PubMed: 17099112]
46. Ferguson AR, Huie JR, Crown ED, et al. Maladaptive spinal plasticity opposes spinal learning and recovery in spinal cord injury. *Frontiers in physiology*. 2012; 3:399. [PubMed: 23087647]
47. Huie JR, Stuck ED, Lee KH, et al. AMPA Receptor Phosphorylation and Synaptic Colocalization on Motor Neurons Drive Maladaptive Plasticity below Complete Spinal Cord Injury. *eNeuro*. Sep-Oct;2015 2(5)

Box. Operational definitions

Dose = amount of active ingredient(s) to produce the desired effect, and the frequency and duration that it is administered. Parameters in pharmaceutical studies include the following:

- *Active ingredient* = ingredient that is biologically active, i.e. will cause the desired response
- *Mechanism of action* = specific biochemical interactions through which the active ingredient leads to the desired response.
- *Half-life* = the time it takes for the active ingredient to lose half of its pharmacologic, physiologic, or radiologic activity. An extension of half-life to rehabilitation is the time it takes for the active ingredient to produce the biochemical interactions. This time will help to determine the appropriate frequency of the intervention (e.g. time for muscle damage and repair in an intervention for muscle strengthening).

Task-specific training = Systematic and repetitive practice of movements or actions in the context of performing a functional task.

- Requires interaction with real objects as one would interact/function in daily life, not just virtual objects or environments.
- Specificity can be defined from the whole task level (e.g. feeding, walking) or at very specific levels (e.g. feeding using spoon and bowl, eccentric muscle activation during walking).
- Intent is to improve functional skills.

Adaptive Plasticity = new neural reorganization or synapses in response to novel experiences or nervous system injury.

Maladaptive Plasticity = aberrant plastic changes that reduce behavior, function and/or learning, or that increase disease symptomology.

Eccentric Motor Control = muscle lengthening under increased mechanical tension.

- Greater neural activity and force production than other forms of muscle contractions.
- Eccentric contractions prime force production of the contralateral muscle

Figure 1.

Group averages from baseline, weekly, post intervention assessments. Groups are named by the total number of repetitions delivered. TW: treatment week, such that TW2 is the assessment taken at the beginning of the second treatment week. Labels are slopes (SEs), expressed as ARAT/wk.

Figure 2.

24-hr accelerometry density profiles from 3 representative individuals, showing the consistency and symmetry in daily upper limb performance in neurologically-intact adults. Color = frequency, with warmer colors indicating more time. A: a representative person; B: a person with more high intensity movements (i.e. higher peak); C: a person with more lower intensity movement (i.e. bright glow in the middle).

Figure 3.

Accelerometry group averages from weekly assessments during the intervention. Labels are slopes (SEs), expressed as Activity Ratio/wk.

Figure 4. 24-hr accelerometry profiles show a lack of change in performance in daily life in one individual with moderate paresis, despite a large change (ARAT = 18 points) in capacity. Colors and labels as in Figure 1. Compare to normal symmetry and colors in Figure 1.

Figure 5.

Locomotor kinematics 28 days after early flat treadmill training (ETT) was delivered with or without high inflammation after contusive SCI and compared to untrained SCI controls (gray) or normal naïve controls (purple). When training was delivered without inflammation in MMP-9 gene knock out (ETT KO) mice, robust locomotor recovery approximating normal levels occurred in trunk instability, toe drags, swing and stance time, ankle velocity in swing and carried over to grid walk (red bars). In contrast, training delivered during high inflammation (ETT WT) produced even greater deficits than had no training be given at all (compare black and grey bars). Published Hansen 2013 Journal of Neuroscience

Figure 6.

Bone-marrow derived monocytes tagged with green fluorescent protein (GFP) invade the lumbar spinal cord segments 1-3 (L1-3) within 24 hrs after midthoracic contusion. Blood vessels labelled with Ly6 are red. Inset shows the image location. Adapted from Hansen 2016 Exp Neurol

Figure 7.

Early treadmill training upregulates inflammatory gene expression and down regulates growth and repair genes in invading myeloid macrophages (MAC) in the lumbar cord after midthoracic contusive SCI. Baseline inflammatory and reparative pathways are represented by microglia (MGL) from normal, naïve mice. (* $p < .05$)

Figure 8.

Late eccentric, downhill (DH; blue) treadmill training improves stepping kinematics (A), fractionated joint movements and interlimb coordination as seen on angle-angle diagrams (B) whereas Flat treadmill (gray) training fails to improve these locomotion features.