Published in final edited form as:

J Neurol Phys Ther. 2017 July ; 41(Suppl 3 IV STEP Spec Iss): S39–S45. doi:10.1097/NPT.000000000000184.

Activity-based Therapy: From Basic Science to Clinical Application for Recovery after Spinal Cord Injury

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Abstract

Background and Purpose—Collaboration between scientists and clinicians effectively accelerated translation of scientific evidence for activity-based therapies (ABT) into rehabilitation. This article addresses the basic scientific findings of activity-dependent plasticity that led to Locomotor Training (LT), an ABT, and its principles to advance recovery in adult and pediatric populations with spinal cord injury (SCI). Expansion to new therapies based on these common principles is highlighted, e.g., epidural stimulation. The article also describes a recently developed measure, the Neuromuscular Recovery Scale (NRS), and its psychometric properties.

Summary of Key Points—LT has led to recovery of walking in some individuals with motor-incomplete SCI even years after injury. Recent studies resulted in individuals with motor-complete SCI regaining some voluntary movements and standing in the presence of epidural stimulation. The level of success for LT and epidural stimulation appears dependent on spinal networks maintaining the appropriate central state of excitability for the desired task. As these new advances in restorative therapies required an outcome measure that measured performance without compensation, the NRS was developed. The NRS has strong psychometric properties in adults, and a pediatric version is under development. Application of LT in children is still novel. Preliminary evidence suggests that LT can improve trunk control, and also foster participation in children with chronic SCI.

Recommendations for Clinical Practice—Activity-based therapies may effectively promote neuromuscular recovery, improve function and participation in adults and children post-SCI.

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Conflicts of Interest: Drs. Behrman, Ardolino and Harkema are founders of NeuroRecovery Ed Inc.

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This work was presented at the IV STEP Proceedings in Columbus, OH in July 2016. Figure 4 was previously published in *Archives of Physical Medicine and Rehabilitation* by our group (seeking permission to reprint).

Evaluation of outcomes with valid measures, such as the NRS, is necessary to document the ability to perform functional tasks, and to assess progress as function improves.

Introduction and Scientific Basis of Activity-Based Therapies

The translation of scientific evidence into clinical practice can be accelerated by bringing scientists and clinicians into the same environment. Working together, these disciplines can promote an approach that encompasses the continuum of care and cure. “Care” entails providing rehabilitation across all healthcare settings: acute care, inpatient rehabilitation, outpatient rehabilitation, community fitness and wellness and integration, whereas ‘cure’ relies on partnering with basic and clinical scientists to advance evidence for clinical decision-making and practice. In some centers, partnerships across acute care, in-patient rehab, out-patient clinical facilities and the the academic university setting provide an environment wherein scientists work within the hospital with clinicians (surgeons, therapists and physiatrists). Together they strive to translate novel scientific findings into the clinic and to collaboratively conduct research in the field of spinal cord injury (SCI).

Institutions that foster partnerships between clinicians and scientists typically have clinical facilities with expert clinicians and animal basic science laboratories with lead scientists in close proximity to one another. This proximity as well as shared seminars, fosters close collaboration and bi-directional translation. In this article, we will provide examples of how novel scientific knowledge has been translated into ABTs to promote recovery and more sensitive, valid and useful outcome measures. ABTs are based on activity-dependent plasticity, changes in the neuromuscular system that are driven by repetitive activity below the level of lesion. We will also describe how these approaches have recently been extended into the population with pediatric-onset SCI to provide cutting-edge clinical care and inform practice via research.

The process of intervention development described in this article is the product of six collaborating rehabilitation centers that are part of the Christopher and Dana Reeve Foundation NeuroRecovery Network (NRN).¹ The NRN’s mission is to develop and expand access to ABTs based on current scientific evidence to promote functional recovery and improve the health and quality of life for people with paralysis. Our approach is to utilize results from basic animal and human studies, case studies, case controlled studies, controlled and randomized large cohort studies synergistically rather than adhering strictly to the hierarchal levels of evidence (Figure 1) to advance evidence-based practice. The NRN implements the standardized intervention developed in collaboration with hospital administrators, physicians, occupational and physical therapists with continuous interaction with the scientists to optimize the translation of the new knowledge.

In the NRN approach, new ABTs are developed from the body of scientific evidence and standardized and evaluated in the clinic. The ABT is then extensively evaluated using available outcome measures and documented in a network-wide clinical database. Recognizing limitations in the current classification systems and measurement tools for persons with SCI, the NRN team collaboratively developed the Neuromuscular Recovery Scale (NRS).² This new outcome measure is used by all sites across the NRN to assess

performance of functional tasks without behavioral compensation or assistance.² In this article, we will discuss the basic scientific findings that led to Locomotor Training (LT) as an ABT and how the principles that underlie this intervention can be expanded to other ABT.

As noted previously, ABTs are based on activity-dependent plasticity (Figure 2). After SCI that results in paresis or paralysis, activity-dependent plasticity can be driven by neuromuscular activation below the injury, either intrinsically using task-specific sensory cues or extrinsically by using stimulation which is the basis for LT. Neuromuscular electrical stimulation using non-standard parameters, and epidural stimulation with repetitive task-specific training are now under study for upper extremity, trunk, and lower extremity movements as well as standing and stepping.³⁻⁷ More recently the central state of excitability of the spinal cord has been shown to be a critical factor in recovery, not only of locomotion, but of voluntary movement even in those with the most severe injuries.⁴

ABT requires neural retraining with task-specificity predominantly provided by appropriate sensory cues and intense, repetitive practice. Intense refers to the number of sessions (e.g., typically greater than 60), daily therapy sessions, and length of session being 1.5 hours/day. The level of success is dependent on the spinal networks maintaining the appropriate central state of excitability for the desired task. The “retrained” nervous system then must adapt in the home and community for functional integration.

The human basic science studies of locomotion^{6,8-9} showed that the spinal cord of individuals with International Standards for Neurological Classification of SCI (ISNCSCI), American Spinal Injury Association Impairment Scale¹⁰ (AIS) classifications A and B could interpret complex sensory signals related to load and speed during stepping. Applying these findings to LT interventions eventually led to recovery of walking in individuals with motor-incomplete SCI (AIS C and D) even years after injury.¹¹ However, not all individuals with motor-incomplete SCI recovered standing and walking, and to our knowledge no person with AIS A or B classification has recovered walking even with intense (i.e., daily 1.5 hours training and greater than 60 sessions) LT. These experiments in humans^{6,8-9} demonstrate that the spinal networks are sophisticated, are strongly influenced by sensory input, and can respond to task-specific training. Adaptability to the community environment, however, was limited to those with motor-incomplete SCI.

The most recent series of human basic science experiments using epidural stimulation^{3-4,7} were originally designed to better understand the properties and capacity of the human spinal cord with the focus on stepping patterns. Stimulating the spinal cord itself provided more sensitive activation of the neural tissue and would enable more direct evidence of the mechanisms of the human spinal cord.^{3-4,7} Unexpectedly, the first individual with the epidural stimulation implant was able to stand independent of physical assistance within the first week following stimulation. Subsequent findings showed that three more individuals were able to stand independently⁷ and even more surprising, voluntary movements of the legs and trunk also could be elicited, but only in the presence of constant epidural stimulation.⁴ All of these behaviors required different epidural stimulation configurations (amplitude, frequency, pulse width and assignment of anode and cathode to electrodes).^{4,7} We interpret these findings to provide further evidence that the human spinal networks,

when achieving the appropriate central state of excitability (in this case presumably via the epidural stimulation) can integrate complex information from the environment and from supraspinal centers to then execute movement. We hypothesize that the details of movement are controlled at the level of the human spinal cord since in these individuals motor supraspinal influence could not be detected with any measure (without epidural stimulation).⁴

Epidural stimulation is an experimental model, however the current understanding of the complex mechanisms and capacity of the human spinal cord can be used to improve and develop ABTs. LT when administered in the presence of a sufficient level of supraspinal influence conceivably drives both the central state of excitability and task-specific retraining by maximizing weight bearing on the legs, optimizing sensory cues, optimizing kinematics and maximizing recovery and minimizing compensation.¹² These training principles can be utilized in physical and occupational therapy, as well as provide a guide for the patient/family in selecting activities and means in the home and community that support recovery. While the treadmill environment is advantageous for intense delivery and control of task-specific sensory input, the principles can be used outside of this environment to advance and promote activation below the lesion. Expanding staffing resources, equipment, and standardization of the therapy are advantageous to successful delivery of the intervention. Future clinical studies of surface neuromuscular stimulation that employ these principles may provide more recovery than previously shown and a more accessible therapy.

Classification of SCI and Measuring Recovery

With new advances in restorative rehabilitative therapies, there is a growing need to change the way in which we classify and assess neuromuscular capacity in the SCI population. Since 1982, the ISNCSCI has been the gold standard for classifying the neurological level and severity of injury in spinal cord injuries.¹⁰ This exam provides the clinician with a standardized method of testing SCI and describes the level of impairment as either complete (AIS A), sensory-incomplete (AIS B), motor-incomplete (C and D), or normal (AIS E).¹⁰ The ISNCSCI has been used often in research as a means to compare subjects with similar severity of injury. However, early data from the NRN demonstrated that there is variability in the functional abilities of subjects with AIS C and D injuries. For example, examination of performance of these persons with motor-incomplete SCI on the Berg Balance Scale (BBS) over time revealed scores that spanned the entire breadth of the scale. This variation did not reduce when this sample was divided into groups by AIS classification. In order to be able to make comparisons across groups in research studies, or make clinical predictions, a tool that can classify persons according to activity domain, in addition to impairment, is needed.

The Neuromuscular Recovery Scale (NRS) was initially developed by researchers and clinicians in the NRN between 2000 and 2008.² The initial purpose of the NRS was to classify persons with SCI into phases of neuromuscular recovery based upon the individual's performance on a series of functional tasks. The initial version of the NRS included 11 tasks that are scored on 12 categories, which have been described elsewhere.² When evaluating a person's performance on each of these tasks, the NRS assesses how the person performs the

item, not merely if the patient is independent in completing the task. The scale emphasizes the use of appropriate kinematics (i.e., pre-injury movement patterns) and disallows compensatory motions.² The person's ability to attain and maintain appropriate posture and kinematics at the upper trunk during each of the tasks is assessed first, followed by the pelvis, and then the lower extremities. After each task has been tested, the individual receives both an overall phase score, and a total NRS score.^{13–14}

The NRS reduces the variability of performance measures when compared to the ISNCSCI.² Figure 3² demonstrates the variability in performance on the Berg Balance Scale that is seen when just the AIS classification is used. When each AIS group is subdivided into NRS phase, then that variability decreases. Thus, assessing an individual using the NRS provides a more sensitive estimate of the person's neuromuscular capacity.

The initial purpose of the NRS was as an additional classification tool.² However, early investigations into the scale showed that changes in the NRS were correlated to changes in other functional outcome measures, indicating that the NRS could be used as an outcome measure to assess functional capacity.² Much has been written about capacity measures for the SCI population, including the Functional Independence Measure (FIM), The Walking Index for Spinal Cord Injury II (WISCI II), the 10-Meter Walk Test (10MWT), and the 6-Minute Walk Test (6MWT).¹⁵ All of these outcome tools measure capacity as they are tested in a standardized environment, yet they also allow for the use of compensatory strategies such as bracing or assistive devices. It is only by quantifying the quality of the movement, and relating this back to pre-morbid function, that we can truly determine the effect of activity-based interventions. Thus, by assessing how an individual performs a movement, the NRS aims to more fully assess neuromuscular recovery.

An ideal outcome measure must have strong psychometric properties. The NRS has been found to have strong test-retest reliability (Spearman correlation coefficients of 0.92–0.99)¹⁶ as well as high inter-rater reliability (Kendall coefficient of concordance 0.90).¹³ The construct validity of the original NRS was established using Rasch analysis,¹⁷ which revealed that the NRS stratifies individuals with all AIS classifications into 5 distinct strata. No floor or ceiling effects were found for the NRS, and the scale also demonstrated a logical order of item difficulty.¹⁷ In addition, the NRS was found to be a stronger predictor of recovery than AIS classification when measuring the change in performance of persons with motor-incomplete SCI on the BBS, 6MWT and 10MWT.¹⁸

Recently, the NRS was modified to remove one of the treadmill items, and add 4 upper extremity items.^{14,19} The responsiveness of this expanded version of the NRS was compared to 6 other outcome measures, and the NRS was the most significantly responsive tool.¹⁹ This version was also more responsive to change than the upper extremity motor score (UEMS) and lower extremity motor score (LEMS) of the ISNCSCI, and the NRS continues to correlate with other outcome measures even if the items tested in the body weight support and treadmill environment are removed from the scale.¹⁴ While the NRS has strong psychometric properties in adults with SCI, the scale needed to be adapted to be age-appropriate for use in children. Children present with inherently different movement

strategies across development. Therefore, the development of a pediatric version of the NRS was warranted.²⁰

The Pediatric Neuromuscular Recovery Scale (Peds NRS) was developed by clinicians and researchers with pediatric expertise and consists of 13 items graded on a 12-point scale.²⁰ The Peds NRS is similar in concept to the adult NRS in that it disallows compensation. The content validation of the Peds NRS was established through the use of a Delphi process.²⁰ An inter-rater reliability study among clinicians completing on-line standardized training in use of the Peds NRS and rating children with SCI aged 2 to 12 years was recently completed and results are forthcoming. Future investigations for both the adult NRS and the Peds NRS include further analysis of the psychometric properties and responsiveness of the Peds NRS. The use of the adult NRS and Peds NRS in other neurological populations is also being investigated.

Activity-based Therapy in Pediatric SCI

Translational research via experimental models of SCI has led to proof-of-principle work in the human condition of adult SCI and provided physiologically-based evidence for development of ‘activity-based therapies’.^{21–24} While research with adults may be highly relevant to the pediatric population after SCI, there are critical considerations for application to children, e.g., musculoskeletal development. Application of LT in children is still relatively novel. To explore its potential benefit in the pediatric population, four questions are posed and discussed in this article:

1. Do children improve after SCI and our current rehabilitation approach?
2. What instruments are used to predict outcomes for children with SCI?
3. Can a ‘recovery-based’ intervention (i.e., ABT), aimed at activating the neuromuscular system below the lesion, alter the known trajectory of outcomes for children after chronic SCI and change participation?
4. Is there a pediatric advantage or disadvantage for activity-dependent plasticity?

First, do children improve after SCI and our current rehabilitation approach? The devastating impact of SCI and paralysis is similar in adults and children requiring external devices to support sitting, standing, and mobility. The impact on other physiological functions is also similar regardless of age, e.g., bladder, cardiovascular, respiratory, integument. Children, however, are uniquely at risk for developing scoliosis and hip dysplasia after SCI. Those injured at a very young age (< 5 years) experience increased risk for scoliosis (96%), hip dysplasia (57%), pressure sores (41%), and autonomic dysreflexia (34%)²⁵ with continued risk of hospitalization into adulthood.²⁶ Strategies to prevent scoliosis and hip dysplasia have not led to optimal results.^{27–29} Children undergoing spinal fusions (67%) are at further risk for infection, as well as decreased function and mobility.²⁸ Activation of trunk muscles and active load-bearing during critical years of maturation and growth may reduce the incidence of these skeletal complications. Our current rehabilitation approach focuses on management of paralysis as opposed to an approach to alter the state of paralysis. The

approaches have predominantly been orthopedic to promote alignment and compensation-based rehabilitation to teach adaptation strategies and behaviors for daily function.

Second, what instruments predict outcomes for children after SCI? As is the case with adults, outcomes for children with pediatric-onset SCI are predicted based on the individual's ability to demonstrate voluntary control of muscle activity below the level of the injury.^{30–33} Children want to move, and children without disability move abundantly. One hour of vigorous activity per day is recommended to promote muscle, bone and aerobic health in typically developing children without disability.³⁴

In comparison, the primary rehabilitation interventions for children with SCI stabilize them in positions that limit or restrict trunk, leg and/or entire body movement, e.g., standers, wheelchairs, braces. Medical interventions used to manage spasticity and range of motion (e.g., botox injections, baclofen, and bracing) add to the prevailing paralysis and restrict movement. The sedentary life post-paralysis is compounded by the current approach to rehabilitation.^{32–33,35–37} Furthermore, significant 'natural recovery' is neither expected nor reported for individuals with chronic SCI, i.e., greater than 12–18 months post-injury.³⁸ Children with chronic injuries are not expected to get better, and parents are often given little to no hope for recovery. With the AIS as the 'gold standard' and sole tool for prediction of outcomes, rehabilitation remains predominantly compensation-based.

Third, can a 'recovery-based' intervention (i.e., ABT) aimed at activating the neuromuscular system below the lesion alter the known trajectory of outcomes for children after chronic SCI and lead to changes in participation? We have observed unexpected outcomes in three children with chronic SCI (one described in a published report³⁹, and additional unpublished clinical data) following participation in a standardized protocol of locomotor training.¹² In all three cases improvements were unexpected because time post-injury exceeded the period of expected natural recovery (16, 20, and 24 months), the children had level of injury (C6; C3-7, T4-T9) wherein recovery could not be attributed to axonal regrowth following lower motoneuron damage, and all had low baseline mobility status (all non-ambulatory and only the second child could crawl)

With locomotor training each child advanced in a specific way: 1) from non-ambulatory to ambulatory with posterior walker, 2) from curved sitting posture and inability to use arms even to prop sit to upright sitting and using arms for lifting and moving items, and 3) from inability to stand or step to ability to stand with posterior walker and to step wearing support harness with overhead support/walker. The second child, furthermore, progressed from using a power wheelchair with chest and waist belt to propelling a manual wheelchair with only a seat belt and to being able to roll and come to sit.

The number of therapy sessions for the three children was 76, 131, and 80. The effect of the intervention appears somewhat robust for this varied range of age at injury and etiology: 3 years 6 months due to gunshot wound; 2 months 24 days due to ischemic insult; and in utero due to neuroblastoma. In all cases, there was no change in AIS score or voluntary movement accounting for improvements. Improvements, however, were observed in the Segmental Assessment of Trunk Control.⁴⁰ One child (second child) pre-training scored 'no head

control' and post-therapy exhibited trunk control to below the ribs. With ABT, the third child gained trunk control from the level of the axillae down to the mid-thoracic segment. Parent report further indicated meaningful changes in participation in the home and community for each child. For instance, a mother reported that her child now stood and explored the kitchen drawers, another mother was now able to sit her child on her hip and carry her with one arm, and a third child was now able to stand independently with a walker, watch TV and eat pizza. While only clinical report, these outcomes point to the potential positive impact of ABT in pediatric-onset SCI.

Fourth and last, is there a pediatric advantage or disadvantage for activity-dependent plasticity? Several aspects may point to a pediatric advantage. Regardless of injury etiology, time since injury, age at onset of ABT, and developmental experience at time of injury, all three children with chronic SCI and receiving ABT demonstrated meaningful, yet unexpected improvements relative to the trajectory of usual outcomes after SCI. The particular emphasis on age-appropriate 'play' during therapy often generates excitement and motivation, potentially raising the child's central state of excitability and the probability of a motor response. Such a vantage is unique to the 'play' state of children. The historical and current approach to rehabilitation for children with SCI has focused on changing the environment or task to achieve support and mobility via compensation.^{32–33,41} With ABT as a recovery-based intervention, the focus is on changing the child's intrinsic neuromuscular capacity. Function also improves in the home and community in concert with the child's own exploration of this new capacity in play and daily activities. Future work in pediatrics must address not only immediate benefit, but also the long-term implications for participation and health with potential reduction in health-care utilization.

Recommendations for Clinical Practice

The activation of the central nervous system coupled with intense task-specific practice has become the foundation for therapeutic interventions targeting recovery. Both adults and children with SCI demonstrate the potential to benefit from such therapies. Increasing the accessibility of therapeutic interventions to all ages is paramount and raises unique challenges in the developing and growing child. Ongoing scientific inquiry, clinical translation, and standardized assessment may lead to discovering that even more recovery is possible, even in those living with chronic paralysis. Our experience is that the collaboration of scientists and clinicians throughout not only the scientific process but also into the clinic promotes a more effective and rapid translation of findings into practice.

Acknowledgments

Sources of Funding for the work:

Craig H. Neilsen Foundation

Congressional Medical Program Department of Defense

NIH-NICHD

Kosair Charities

Christopher and Dana Reeve Foundation NeuroRecovery Network

Leona M. and Harry B. Helmsley Charitable Trust

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Figure 1.
Synergy of scientific evidence across sources for translation and clinical decision-making.

Figure 2.
Key elements and basis for activity-based therapies

Figure 3.

Performance on the Berg Balance Scale in NeuroRecovery Network participants, subdivided by AIS and NRS classifications.² (AIS = American Spinal Injury Association Impairment Scale, NRS = Neuromuscular Recovery Scale)