Changes in Supraspinal Activation Patterns following Robotic Locomotor Therapy in Motor-Incomplete Spinal Cord Injury

Patricia Winchester, Roderick McColl, Ross Querry, Nathan Foreman, James Mosby, Keith Tansey, and Jon Williamson

Objectives. *Body weight–supported treadmill training (BWSTT) is a task-specific rehabilitation strategy that enhances functional locomotion in patients following spinal cord injury (SCI). Supraspinal centers may play an important role in the recovery of over-ground locomotor function in patients with motor-incomplete SCI. The purpose of this study was to evaluate the potential for supraspinal reorganization associated with 12 weeks of robotic BWSTT using functional magnetic resonance imaging (fMRI).* Methods. *Four men with motor-incomplete SCI participated in this study. Time since onset ranged from 14 weeks to 48 months post-SCI injury. All subjects were trained with BWSTT 3 times weekly for 12 weeks. This training was preceded and followed by fMRI study of supraspinal activity during a movement task. Testing of locomotor disability included the Walking Index for Spinal Cord Injury (WISCI II) and over-ground gait speed.* Results. *All subjects demonstrated some degree of change in the blood-oxygen-level-dependent (BOLD) signal following BWSTT. fMRI results demonstrated greater activation in sensorimotor cortical regions (S1, S2) and cerebellar regions following BWSTT.* Conclusions. *Intensive task-specific rehabilitative training, such as robotic BWSTT, can promote supraspinal plasticity in the motor centers known to be involved in locomotion. Furthermore, improvement in over-ground locomotion is accompanied by an increased activation of the cerebellum.*

Key Words: *Locomotor training—Functional magnetic resonance imaging—Supraspinal plasticity—Motor cortex—Cerebellum—Spinal cord injury*

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Winchester P, McColl R, Querry R, Foreman N, Mosby J, Tansey K, Williamson J. Changes in supraspinal activation patterns following robotic locomotor therapy in motor-incomplete spinal cord injury. *Neurorehabil Neural Repair* 2005;19:313–324.

DOI: 10.1177/1545968305281515

Body weight–supported treadmill training (BWSTT) is a task-specific rehabilitation strategy that has been shown to enhance functional locomotion in patients following neurological insult such as stroke[1] and spinal cord injury (SCI).[2-5] A portion of the patient's body weight is supported while the patient is assisted to walk on a motorized treadmill with the goal of providing normal kinematic and temporal cues during walking. BWSTT is based on practicing a normal physiologic gait pattern, with attention to the ideal kinematic and temporal aspects of gait.[3,6,7] To replicate a normal gait pattern, 2 to 3 physical therapists are needed to safely conduct the task-specific training sessions to control or assist with trunk and limb kinematics. Because close to normal gait speeds are needed to maintain the normal temporal aspects of locomotion, the training can be physically taxing, and step-to-step consistency is difficult to maintain.

Because of the drawbacks to manual locomotor training, scientists and engineers have developed robotic devices that can assist gait rehabilitation.[8-11] The goals are to reduce therapist physical demand and time, improve repeatability of stepping kinematics, and increase volume of locomotor training. The Lokomat Driven Gait Orthosis® (DGO) developed by Hocoma (Hocoma AG, Zurich, Switzerland) consists of a position-controlled robotic gait orthosis and the Lokolift body weight support system. Position control refers to the robotic device, rather than the therapists, controlling limb position in a temporal pattern appropriate for stepping using imposed guidance forces. The robotic orthosis is synchronized to the treadmill speed so that the robotic device guides the legs through preprogrammed physiological gait patterns while the subject experiences near-normal proprioceptive input during limb loading.

There have been multiple reports of the spinal cord contribution to locomotion in cats[12-15] and humans.[16-18] Although a cat with a thoracic spinal cord transection can learn to step on a treadmill with trunk support, the animal does not demonstrate the ability to transfer this skill to walk over ground.[19] Similarly, patientss with a motor-complete SCI may demonstrate improvement in their ability to walk on the treadmill with training, but they do not achieve the ability to walk over ground.[20,21] Only subjects with motor-incomplete SCI demonstrate improvement in their ability to walk over ground following BWSTT, suggesting that supraspinal centers play a critically important role in the recovery of over-ground locomotor function. It is currently not known what changes might occur within the higher brain centers of patients with a motor-incomplete SCI showing improved locomotor function following BWSTT.

Functional magnetic resonance imaging (fMRI) can be used to assess patterns of supraspinal activation by using the blood-oxygen-level-dependent (BOLD) signal to make inferences about neural activity. Changes in activated sensorimotor regions of interest (ROIs) can be related to improvement in function following a specific rehabilitation intervention.[22] Specifically for BWSTT, these ROIs would include the sensorimotor centers associated with walking. Fukuyama and colleagues[23], using single photon emission computerized tomography (SPECT), reported activation of the supplementary motor area (SMA), medial primary sensorimotor area, the basal ganglia, cerebellar vermis, and the visual cortex in normal subjects while walking. Miyai and colleagues[24] used near infrared spectroscopy to demonstrate that the premotor cortex and SMA were involved in the restoration of gait in patients following a cerebrovascular accident. Dobkin and colleagues[25] used voluntary ankle dorsiflexion as a paradigm during fMRI to assess motor learning and functional gains during 10 weeks of BWSTT in chronic stroke subjects. They were able to demonstrate changes in cortical activation patterns in the cingulate motor cortex and secondary sensory area related to improvement in walking in 4 stroke subjects. However, a repeated measures functional imaging study involving recovery of locomotion in patients with SCI has not been reported.

Although it is not possible to have the subject walk within the magnet, it is possible to have him or her perform a motor task that is related to walking. The motor task used to assess changes in cortical activation with fMRI associated with functional gains following training must incorporate an essential component of the training. In the case of manually assisted BWSTT, ankle dorsiflexion is a good motor task in that it incorporates an essential component of the ankle during swing limb advancement.[25] Unlike manually assisted BWSTT, training in the Lokomat robotic device has been shown to dampen the EMG activity of the anterior tibialis muscle compared to the EMG activity observed with manually assisted BWSTT.[26] Foreman and colleagues[26] demonstrated that the EMG pattern of the soleus muscle of the lower leg was activated during BWSTT on the Lokomat robotic device and was equivalent to the EMG activity observed during manually assisted BWSTT. Ankle plantar flexion and toe flexion could serve as a useful probe in that this motor task is important during the stance phase of gait. The soleus muscle is active from 6% to 52% of the gait cycle, with the peak at 40% of the gait cycle in normal subjects. Similarly, the flexor digitorum longus and flexor hallucis longus muscles are active from 13% to 54% of the gait cycle in normal subjects.[27]

The goal of this study was to evaluate the potential for supraspinal reorganization associated with 12 weeks of BWSTT using fMRI and to further determine if the potential changes in patterns of supraspinal activation were associated with functional gains produced by locomotor training. Specifically, differences in sensorimotor networks (e.g., sensorimotor cortex, cingulate motor cortex, and cerebellum) activated during ankle plantar flexion and toe flexion before and after a 12-week intervention period of BWSTT is presented in 4 subjects with motor-incomplete SCI.

METHODS

Subjects

The subjects were 4 male patients with tetraparesis secondary to an isolated traumatic SCI. The patient population in this study was a sample of convenience made up of subjects who had been referred for BWSTT and were between 20 and 49 years of age. The patients ranged from 14 weeks to 4 years post-SCI. The 4 patients were evaluated to ensure that they complied with the following inclusion criteria: 1) intact lower motor neurons, 2) lower extremity range of motion sufficient to allow upright stance, and 3) muscle and joint stability available for weight bearing at lower extremities. None of the subjects had a history of long

bone fractures secondary to osteoporosis, decubitus ulcer(s) that interfered with harness support or walking (feet), or weighed greater than 250 lb. Written informed consent was obtained from all subjects, as approved by the institutional review board at the University of Texas Southwestern Medical Center. Each subject was evaluated and classified according to his neurological level and impairment level using the American Spinal Injury Association (ASIA) standards[28] for neurological and functional classification. The lower extremity motor score was determined for each subject. In accordance with ASIA guidelines, manual muscle testing was done on the 5 key muscle groups, hip flexors, knee extensors, ankle dorsiflexors, great toe extensors, and ankle plantar flexors, and then summed to determine the lower extremity motor score.

The 4 subjects described in this study met all inclusion and exclusion criteria. They presented with a mixture of acute and chronic injuries and varying presentation of locomotor disability. All patients and their physicians agreed that medications would not be changed throughout the course of the 12-week training program. The 4 participants were not involved in any other therapy during the study. A description of each patient follows.

Patient 1 was a 45-year-old man with a C5 incomplete SCI from trauma 14 weeks previously. His initial ASIA classification at entry into the study was C. His lower extremity motor score was 10 on the right and 13 on the left. The patient's medications at the time of entry into the study included Neurontin, 300 mg 3 times daily. This dosage was maintained throughout the 12 weeks of BWSTT. Patient 1 was unable to ambulate but was able to stand with assistance upon entry into the study.

Patient 2 was a 20-year-old man with a C6 incomplete SCI secondary to a motor vehicle accident 6 months previously. His initial ASIA classification at entry into the study was D. His lower extremity motor score was 9 on the left and 13 on the right. The patient was taking 10 mg of Baclofen 3 times daily at the time of entry into the study. This dosage was not changed throughout the 3-month study period. Patient 2 was able to ambulate initially with a walker, a right ankle foot orthosis (AFO), and required physical assistance.

Patient 3 was a 49-year-old man with a C5 incomplete SCI secondary to a motorcycle accident 1 year previously. His initial ASIA classification at entry into the study was C. His lower extremity motor score was 13 on the left and 9 on the right. The patient's medications at the time of entry into the study included an intrathecal Baclofen pump. The intrathecal pump had been placed 4 months before the study, owing to severe spasticity. The dose was set at 320 μg per day 4 weeks before entry into the study and did not change throughout the 12 weeks of BWSTT. Patient 3 was unable to ambulate or stand.

Patient 4 was a 44-year-old man with a C6 incomplete SCI from a biking accident 4 years previously. His initial ASIA classification at entry into the study was C. His lower extremity motor score was 6 on the left and 9 on the right. This patient was not taking any medications at the time of entry into the study and was unable to ambulate or stand.

Intervention

All participants were trained at the Spinal Cord Injury Laboratory at the University of Texas Southwestern Medical Center. Each subject was scheduled for a 60-min session 3 times weekly for 12 weeks. The Lokomat DGO was utilized to provide the locomotor training and was used in combination with a Woodway treadmill (Woodway GmbH; Steinackerstrasse 20, Weil am Rhein, Germany) as previously described.[29] All the participants were fitted with a weight-supporting harness that was placed around the hips and abdomen and fastened to fit snugly enough to minimize upward slipping of the harness when body weight suspension was applied. The patient in a wheelchair was wheeled up onto the treadmill by way of a ramp. The harness was attached to the cables on the body weight support system. The subject was then assisted to stand on the treadmill by the Lokolift body weight support system using a motor-driven winch. The DGO was secured to the patient by straps across the pelvis and chest. Femoral and tibial length measurements were used to adjust the robotic force arm and robotic drive motor positions for the knee and ankle joints. Ankles were positioned in neutral dorsiflexion to assist in swing limb clearance with the use of spring-assisted elastic straps. Once the patient was set up, the treadmill was started and the subject was lowered to the treadmill. The Lokomat DGO uses computer-controlled motors that are synchronized with the speed of the treadmill. Motorized actuators at both knees and hips are programmed to produce a normal physiologic gait pattern with attention to reproduce the normal kinematics of gait.

Table 1. The Percentage of Body Weight–Supported and Training Treadmill Speed at the Beginning and End of BWSTT for Each Patient

Patient	Body Weight Supported (% body weight)		Treadmill Speed (kmph)	
	Initial	Final	Initial	Final
1	53	10	2.0	3.2
2	35	0	2.0	2.6
3	59	42	2.0	2.3
4	55	44	2.0	2.5

BWSTT = Body weight–supported treadmill training.

The level of body weight support was determined by the minimum unweighting needed to enable assisted stepping on the treadmill. The lowest level of body weight support that allowed upright standing without more than 15° of knee flexion and without upper extremity support was selected. This level initially ranged from 35% to 59% in this group of 4 subjects but was reduced to 0% to 44% by the end of the training period. Treadmill speed was initially set at 2.0 kmph but was increased when reciprocal stepping could be achieved without a problem with limb clearance. Maximum treadmill speed was 3.2 kmph. At the end of the 12-week training program, treadmill speeds ranged from 2.3 to 3.2 kmph in this group of patients. The training parameters for each of the 4 patients are given in Table 1.

During the actual training, a biofeedback system on the Lokomat system displayed the patient's effort during locomotor training in real time to both the investigator and the patient. Force transducers at each of the hip and knee joints measured the interaction between the patient and the Lokomat DGO during walking. This measuring allowed direct feedback to the patient while actually walking, and the patients were cued to actively move with the DGO. This enhanced the patient's motivation to do as much work as possible and minimized passive locomotor training.

Over-ground walking was initiated only when the subject was able to walk on the treadmill with less than 20% of body weight supported. Still, treadmill training was continued for a minimum of 20 min per session followed by gait training over ground. Ankle-foot orthoses were used during over-ground locomotor training if indicated to provide dorsiflexion during swing limb advancement or to assist tibial stability during the single-limb support phase of walking. The therapist chose the appropriate assistive device based on the patient's balance and endurance. Patients were released to begin over-ground walking in their home setting only when independence had been achieved with crutches or canes.

Procedure

All subjects were trained with BWSTT for 12 weeks, preceded and followed by fMRI as well as testing of locomotor disability, including the Walking Index for Spinal Cord Injury (WISCI II),[30,31] over-ground gait speed, and assistive device usage. The preintervention testing was done once, 1 to 2 d before the initiation of BWSTT. Postintervention testing was done immediately 1 d after the 12-week training period was completed. No other gait therapy or additional nongait physical therapy was given to these patients during the study.

OUTCOME MEASURES

Imaging Protocol

The MRIs were conducted at the Algur H. Meadows Imaging Center at the University of Texas Southwestern Medical Center using a 1.5 tesla General Electric Signa Horizon NV/i scanner specially designed for neuroimaging research. The NV/i system is equipped with a real-time fMRI acquisition computer, which allows the acquisition of an almost unlimited number of MRI images per acquisition. Approximately 2000 images were acquired during each fMRI, using a whole brain scan protocol with the following technical parameters: TE/TR = 45/2000, number of slices = 18–22, matrix = 64 × 64, FOV = 240 mm, slice thickness/gap = 7.0/0.5. Structural scans (3D SPGR, FOV = 240 mm, matrix = 256/192, 2 mm slice thickness) were acquired to facilitate transformation of the data into the Talairach coordinates system for multisubject analysis.

During the functional imaging, the motor task of ankle plantar flexion and toe flexion was performed using a block design with the subject cued to plantarflex the ankle and curl the toes for 20 s alternated with a 20-s rest period. In each task, a total of 5 rest states and 5 active states were alternated, requiring 200 s of imaging time. This task was performed unilaterally for approximately 10 repetitions (0.5 Hz). The auditory cue, "Switch," was delivered through a headset worn by the subject to trigger movement and rest periods. Soft pads were placed behind the knee and posterior

calf to place the knee in slight flexion and to avoid any pressure to the calcaneus. This positioning allowed the patient to actively move the ankle without overcoming passive resistance possibly caused by the gastrocnemius muscle or by the weight of the foot on the table.

All subjects received instructions and practiced performing the activation task several days before each scanning session. All patients had sufficient strength to actively move their strongest ankle through full range of motion; however, the range of movement was limited in this study to midrange to avoid initiating an extensor muscle spasm and unwanted head movement. Subjects were instructed to plantarflex their strongest ankle to approximately 20° and curl their toes. During practice sessions, the desired ankle motion was determined using a handheld goniometer. Once this position was determined, the ankle was blocked initially at the targeted end range for learning. Practice included moving the ankle and toes to an auditory metronome set at 0.5 Hz to reinforce the desired speed of motion. To ensure that the activation task was unchanged pre- and posttherapy, a research investigator visually monitored the task to ensure that the range and speed of movement was consistent between trials. If the active motion or speed of motion was not consistent, the task was stopped and the subject cued before reinitiating. At times, muscle spasms were observed; however, the occurrence was random, so it was determined that the protocol would minimize any artifact associated with the involuntary spasms. A Velcro head strap was placed across the forehead of all subjects and attached to the head coil assembly to minimize head motion in general.

Ambulation Outcome Measures

The WISCI II was used to assess locomotor disability.[30] The WISCI II ordinal 0–20 scale is based on physical assistance needed and use of orthotic and assistive devices needed to traverse 10 m. Each subject was assigned a WISCI II level in accordance with his impairment before and after the 12-week intervention period. The WISCI II has been shown to be a valid and reliable tool for documenting improvements in ambulation-associated functional limitations.[31]

Gait speed was recorded for each subject who could walk over ground using the commercially available GAITRite system (CIR Systems, Inc.; Havertown, PA). Subjects walked at a self-selected, comfortable speed over a 3.66-m instrumented mat. In addition, the type of walking assistive devices (walker, forearm crutches, cane) was recorded. Use of orthotic devices to walk was recorded including knee-ankle-foot orthoses (KAFOs) and AFOs.

Table 2. Change in Walking Index for Spinal Cord Injury II (WISCI II) and Over-Ground Gait Speed for Each Patient

	WISCI II		Gait Speed cm/s	
Patient	Initial	Final	Initial	Final
1	0	19	*	80.6
2	6	15	23.8	62.0
3	0	6	*	10.5
4	0	0	*	*

*Unable to ambulate at time of testing.

Data Analyses

Following the image acquisition, all data were converted into AFNI format and analysis used the AFNI program (http://afni.nimh.nih.gov/afni) widely used by fMRI research sites. A motion correction was applied to the sequential data to ensure that any slight motion of the head during acquisition was corrected. A 7 mm full width at half maximum smoothing kernel was applied in all axes to the data to remove high-frequency spatial noise, which can give rise to spurious apparent activity. Time-series data during ankle plantar flexion and toe curling motor task were correlated with an ideal hemodynamic function derived from the stimulus and published characterization of the impulse delay in motor cortex ROIs to stimulus. The stimulus course was 20 s active, 20 s rest, repeated 5 times. A superimposition of detected threshold activation was applied onto a T1-weighted volume scan of each subject obtained at the start of each examination and reoriented into the Talairach coordinate system, with 1 mm^3 resolution. The correlation threshold was set to $P = 0.5$.

For each functional scan, a voxel-wise t test compared active and rest states within each brain voxel. All scans were carefully examined for evidence of misregistration. An appropriate Z cutoff value was used to establish a corrected P value of <0.05 to calculate increased areas of activation above threshold in the defined ROI. The specific ROIs for the task employed included the primary sensory and motor areas (S1M1), the cingulate motor area (CMA), and the cerebellum.

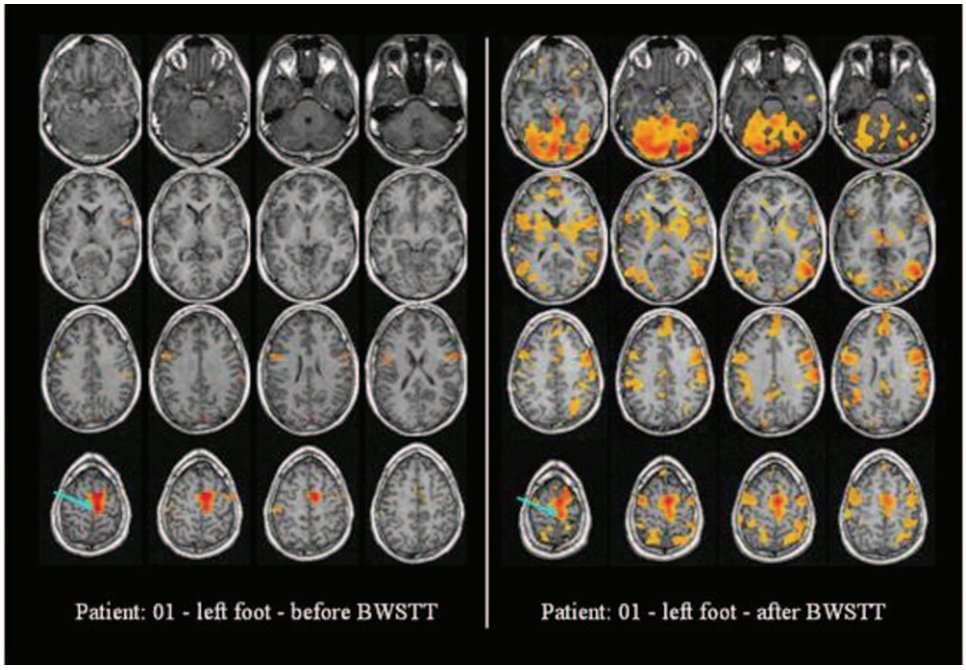

Figure 1. Sequential transaxial slices before and after 12 weeks of body weight–supported treadmill training (BWSTT) beginning at the top of the head (bottom left corner) to the level of the eyes (top right corner). The data are from patient 1 with an incomplete C5 spinal cord injury who achieved independent ambulation with a single-tip cane. The red-orange regions show regions of brain activation corresponding to the voluntary ankle plantar flexion and toe flexion. Arrows indicate location of primary motor cortex for foot and ankle movement.

RESULTS

Changes in locomotor disability, gait speed, and assistive device usage for each patient are described below and are summarized in Table 2. Figures 1 through 4 demonstrate patterns of brain activation pre- and post-BWSTT in each of the 4 patients.

Patient 1

This participant was unable to ambulate initially but was able to stand with assistance. After session 21 (week 7), the patient achieved independent ambulation with bilateral forearm crutches (WISCI = 16) and was released to begin to walk over ground in his home setting. By the end of the 12-week training period, he was ambulating independently with a single-tip cane and no orthotic devices in the community setting (WISCI II = 19). His gait speed was 80.6 cm/s (59.7% of normal). Lower extremity motor score had improved from 10 to 17 on the right and from 13 to 19 on the left. Following 12 weeks of BWSTT, the patient's ASIA classification changed from C to D.

Initially, during left toe flexion and ankle plantar flexion, foci of activation were noted in the left and right S1M1, with a relatively stronger right activity (Figure 1, left panel, row 4). Smaller foci of activation were noted in bilateral CMA (Figure 1, left panel, row 3). Following 12 weeks of BWSTT, there was increased area of activation in the S1M1 areas (Figure 1, right panel, row 4) and increased activation was now noted in the CMA (Figure 1, right panel, rows 3 and 4) and cerebellum (Figure 1, right panel, row 1).

Patient 2

This participant was able to ambulate initially with a walker, a left AFO and physical assistance (WISCI II = 6). He discontinued any over-ground walking until the end of the 12-week study period, at which time he had achieved independent ambulation in the community with a single-tip cane. He required continued use of an AFO, owing to spastic equinovarus posturing of the left ankle (WISCI II = 15). His over-ground gait speed had improved from 23.8 to 62.0 cm/sec (from 17.6% to 46% of normal). His lower extremity motor score had improved from 12 to 17 on the right and from 20 to

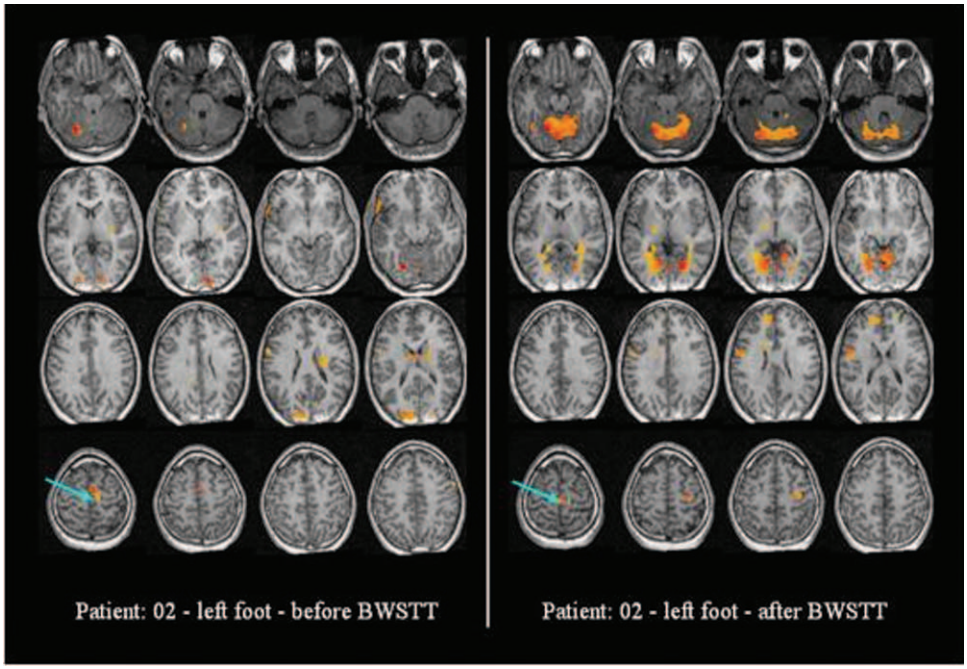

Figure 2. Sequential transaxial slices before and after 12 weeks of body weight–supported treadmill training (BWSTT) beginning at the top of the head (bottom left corner) to the level of the eyes (top right corner). The data are from patient 2 with an incomplete C6 spinal cord injury who achieved independent ambulation with a single-tip cane and left ankle-foot orthosis. The red-orange regions show regions of brain activation corresponding to the voluntary ankle plantar flexion and toe flexion. Arrows indicate location of primary motor cortex for foot and ankle movement.

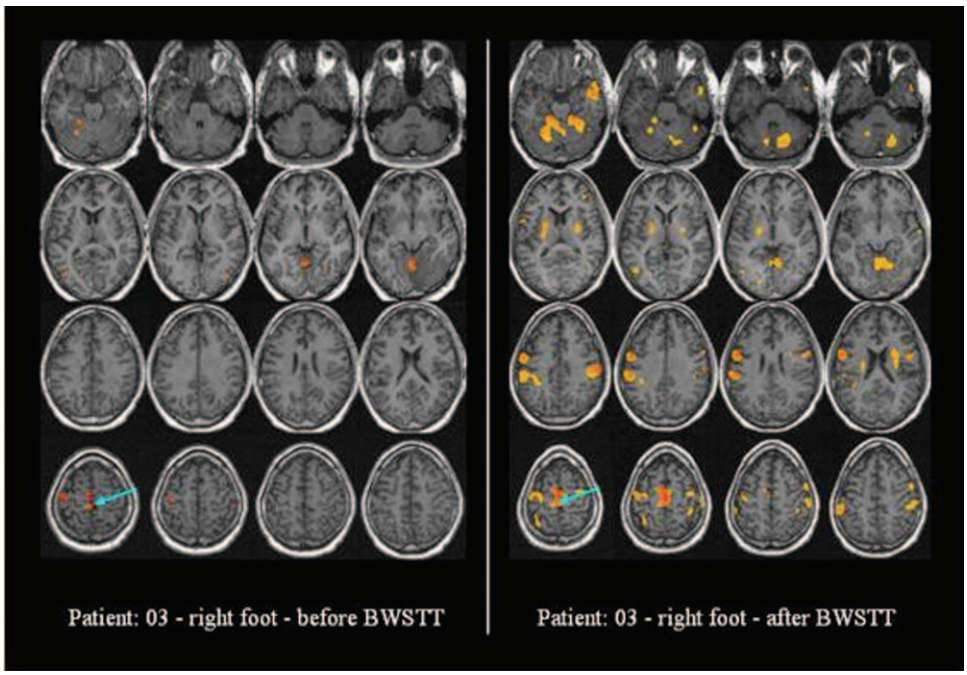

Figure 3. Sequential transaxial slices before and after 12 weeks of body weight–supported treadmill training (BWSTT) beginning at the top of the head (bottom left corner) to the level of the eyes (top right corner). The data are from patient 3 with an incomplete C5 spinal cord injury who achieved limited ability to ambulate over ground with a forearm walker, right ankle-foot orthosis, and physical assistance. The red-orange regions show regions of brain activation corresponding to the voluntary ankle plantar flexion and toe flexion. Arrows indicate location of primary motor cortex for foot and ankle movement.

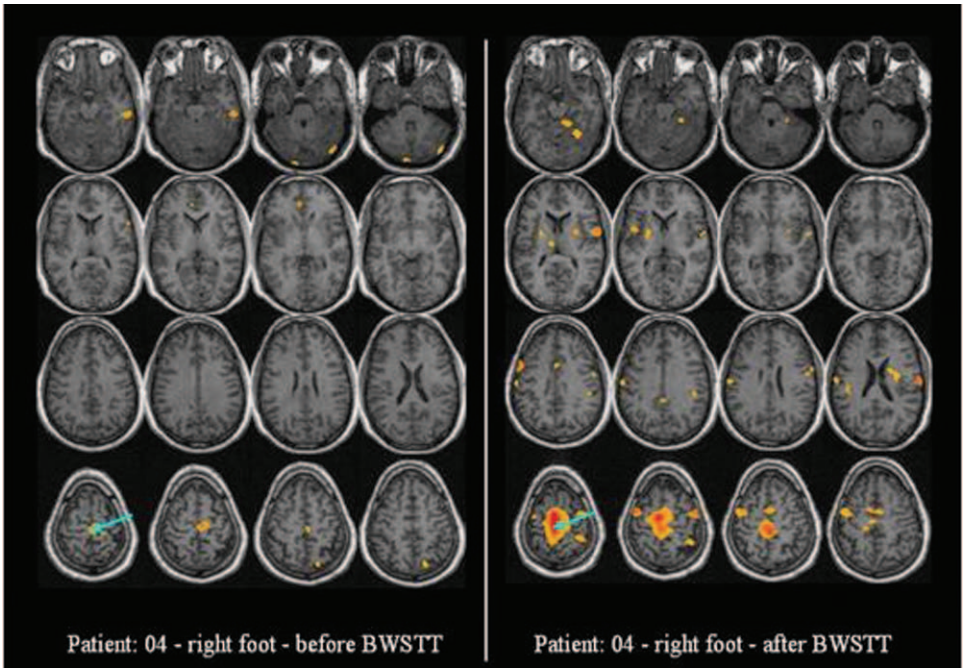

Figure 4. Sequential transaxial slices before and after 12 weeks of body weight–supported treadmill training (BWSTT) beginning at the top of the head (bottom left corner) to the level of the eyes (top right corner). The data are from patient 4 with an incomplete C6 spinal cord injury who did not achieve any ability to walk over ground. The red-orange regions show regions of brain activation corresponding to the voluntary ankle plantar flexion and toe flexion. Arrows indicate location of primary motor cortex for foot and ankle movement.

25 on the left. Following BWSTT, his ASIA impairment level remained D.

Patient 2 demonstrated a small area of activation of the right S1M1 and left cerebellum during left ankle plantar flexion and toe flexion (Figure 2, left panel, row 1 and 4). Following 12 weeks of BWSTT, there was continued activation in the right S1M1 (Figure 2, right panel, row 4) and left CMA (Figure 2, right panel, row 3). Following BWSTT, there was significant increased activation of the bilateral cerebellum (Figure 2, right panel, row 1) during voluntary ankle plantar flexion and toe flexion after 12 weeks of training.

Patient 3

This subject was unable to ambulate or stand initially, but by the end of the 12-week training period, he was able to ambulate with a forearm walker and required physical assistance primarily to advance his right lower extremity. The forearm walker was necessary for this patient to ambulate, owing to nonfunctional strength in the triceps muscles. He also required use of a right AFO for ankle control during swing and stance (WISCI II = 6). His gait speed was 10.5 cm/s and was 7.8% of an age-matched able-bodied person. His lower extremity motor score had improved from 9 to 12 on the left and from 13 to 15 on the right. Following BWSTT, his ASIA impairment level remained C.

Patient 3 demonstrated minimal activation of the left S1M1 and CMA during right ankle plantar flexion and toe flexion (Figure 3, left panel, row 4). Patient 3 demonstrated increased activation of the left S1M1 area with right toe flexion and ankle plantar flexion following 12 weeks of BWSTT (Figure 3, right panel, row 4). In addition, there was significant activation in the bilateral CMA (Figure 3, right panel, row 3) and bilateral cerebellum (Figure 3, right panel, row 1) during ankle and toe movement following training.

Patient 4

This patient was unable to ambulate initially or after the 12-week training period. Following BWSTT, his ASIA impairment level remained C and there were no changes in his lower extremity motor score (left = 6, right = 9). Although no functional change was observed, there was a change in the BOLD signal following 12 weeks of BWSTT. The patient initially demonstrated a small area of

activation in the S1M1 areas with active right toe and ankle plantarflexion (Figure 4, left panel, row 4). Following BWSTT, there was a significant increase in activation in the left S1M1 areas (Figure 4, right panel, row 4). Additionally, there were small foci of activation in the bilateral CMA (Figure 4, right panel, row 3) and cerebellum (Figure 4, right panel, row 1).

DISCUSSION

In this small sample case series, we have observed changes in the supraspinal activation patterns during active toe flexion and ankle plantar flexion in 4 subjects following 12 weeks of robotic BWSTT. A major finding was that all 4 subjects demonstrated some degree of change in the BOLD signal during ankle plantar flexion and toe flexion following 12 weeks of robotic BWSTT. Caution must be taken when interpreting the relevance of the BOLD signal changes in this small sample size; however, this evidence suggests that intensive task-specific training, such as practiced with BWSTT, may induce supraspinal plasticity in patients with a motor-incomplete SCI. Furthermore, this change in supraspinal activation in response to a specific motor task occurred regardless of the time since the patient had sustained his SCI, albeit to varying degrees. Time from onset ranged from 18 weeks to 4 years, and all patients demonstrated increased activation in motor cortices following BWSTT.

All 4 subjects demonstrated activation of the foot and toe area of the sensorimotor cortex following robotic locomotor training. Dobkin and colleagues have previously reported activation of the right foot, leg, and trunk primary sensorimotor region in a subject with a motor-incomplete T6 SCI undergoing training with manual BWSTT.[32] However, a novel finding from this study was that the varying functional gains in ambulatory capacity made by these 4 patients were associated with different patterns of cortical and cerebellar activation and the magnitude of these changes.

Although all participants demonstrated a change in the BOLD signal following training, only those patients who demonstrated a substantial increase in activation of the cerebellum demonstrated an improvement in their ability to walk over ground. Patients 1 and 2 demonstrated the greatest change in cerebellar activation following training, and both achieved independent ambulation over ground with assistive devices. Both subjects were able to give up the use of their wheelchairs for community mobility. Although patient 3 demonstrated increased activation of the bilateral cerebellum following robotic BWSTT, the change in area was not as robust as observed in patients 1 and 2. Patient 3's gain in functional ambulation was limited to walking over ground for short distances with physical assistance. Patient 4, who was unable to obtain the ability to walk over ground following BWSTT, demonstrated very little activation in the cerebellum following training. Patient 4 had the longest time from onset to locomotor training compared to the other 3 patients.

Those patients with the shortest time since onset demonstrated the greatest improvement in both function and motor scores. Although we cannot resolve anatomical differences between subjects in terms of specific ascending or descending pathways across the level of injury and so cannot comment on whether differences in recovery are attributable to these differences, it is striking that the length of time since injury onset may have affected the efficacy of synaptic plasticity within the spinal cord, within supraspinal centers, or between those centers.[33] Those patients with a longer time from onset to time of locomotor training may lack the plasticity necessary to develop and use afferent and descending pathways necessary to benefit from this rehabilitation or may at least not benefit as much as patients with more recent injuries.

The data from these patient cases imply that the pattern of changes in the cerebellar networks may be associated with the functional gains made or the lack of improvement made by the individual patient. The cerebellar activations observed could be related to either the motor learning that occurred during locomotor training or improved performance of the activation task itself. Because there were no differences in the range or speed of motion performing the activation task before and after training, this finding suggests that it was the motor learning that occurred during locomotor training that attributed to the changes noted in the cerebellar activation patterns.

Previously, we reported fMRI data during attempted bilateral toe flexion from a subject with a complete C5 SCI following 12 weeks of manual BWSTT.[34] This subject was 8 months post–complete SCI and demonstrated a greater activation in S1M1 regions and CMA with attempted toe movement following manual BWSTT. Although the activation task is different from that reported in this study, the increased activation in the sensori-

motor cortex was similar to what we observed in this study. Activation of sensorimotor regions following locomotor training is not surprising during attempted movement in a subject with a complete SCI, because there are data demonstrating brain activation for these regions during imagined movement[35-37] and during imagined walking.[38,39] Interestingly, there were no changes within the cerebellar regions with the activation task for this subject with a complete SCI. This subject is similar to our subject 4 who made no functional improvement following locomotor training. The lack of cerebellar activation in this subject and subject 4 may be related to the lack of afferent feedback or lack of plasticity in those systems and suggests the importance of the neocerebellum as a feedback loop monitoring the peripheral afferent inputs for generating the appropriate locomotor pattern. Subjects with increased time between onset of the SCI and the intervention, such as subject 4, may demonstrate attenuated plasticity similar to that seen in subjects with a complete SCI.

These findings are even more interesting when compared to similar studies of treadmill training in a rodent model of incomplete SCI. de Leon and colleagues[40] demonstrated that treadmill training hastens locomotor recovery in rats that have undergone thoracic spinal cord contusions. Treadmill training in these animals also results in changes in gene expression as assessed using microarray technology, and these investigators found that there was approximately a 10-fold greater number of gene expression changes in the cerebellum when compared to the spinal cord or sensorimotor cerebral cortex.[41] Taken together, these human and animal studies provide support for the idea that the cerebellum is an important focus of neural plasticity in response to locomotor training after incomplete SCI and, possibly, the resultant functional recovery.

To relate functional gains following a rehabilitative intervention such as BWSTT to MRI signal changes within sensorimotor regions, the motor task used to activate supraspinal networks during the fMRI must incorporate components of the movements being retrained during BWSTT. We chose the motor task of ankle plantar flexion and toe flexion for the activation paradigm during the fMRI. During normal gait, dorsiflexion torque increases during the single-limb support period of walking until it reaches its peak at terminal stance. Activity of the posterior compartment muscles peaks at this time to resist the substantial dorsiflexion torque.[27] This same muscle activation pattern of the posterior compartment muscles has been demonstrated during BWSTT during both manually assisted and robotic training.[26] Furthermore, we elected to use a motor task that most patients with motor-incomplete SCI could perform. Because the posterior compartment muscles, including the soleus, flexor digitorum longus, and flexor hallucis longus muscles, are innervated by the tibial nerve and receive innervation by sacral segments 1 and 2, most patients with motor-incomplete SCI have some volitional control of these muscles. This allowed a discreet motor task that was trained during robotic BWSTT and minimized the potential for head movement during the imaging.

Central pattern generators have been suggested to be integral in the automatic control of stepping in quadrupedal animals.[7,12-15] Although spinal networks are important for locomotion, supraspinal influences are critical in human locomotion. Human walking may require more supraspinal control because of the postural adjustments necessary for upright bipedal locomotion and the dependence on feedback control.[42] Subjects 1 and 2 recovered the greatest ability to ambulate over ground and also demonstrated the greatest change in the BOLD signal during the activation task following locomotor training compared to subject 4. Subjects 1 and 2 also demonstrated the greatest improvement in their lower extremity motor scores, indicating a high level of residual descending input not shared by subject 4 who was 4 years postinjury.

During human locomotion, the cerebellum is responsible for integrating the feedback from peripheral receptors and spinal central pattern generators with descending motor commands for stepping. The cerebellum adjusts the locomotor pattern via input to several brain stem nuclei, most important, the reticulospinal system, and with feedback to the sensorimotor cortex and basal ganglia.[43] The cerebellum receives sensory information about ongoing movement from muscle spindles, golgi tendon organs, and flexor reflex afferents via spinocerebellar pathways, which also carry a "copy" of the output of the spinal central pattern generator to the cerebellum.[44] The cerebellum also receives a version of the descending motor commands for stepping from the cortex via corticobulbar projections to brainstem nuclei that then communicate with the cerebellum, such as the reticular formation, the red nucleus, and the pontine nuclei. It is thought the cerebellum compares the information from the ascending and

descending pathways and adjusts its output accordingly. Without this ability to compare afferent feedback from the periphery and preferred values set by the spinal central pattern generators with descending commands, functional overground locomotion is not executed normally.

In the subjects reported here, it is not clear how much cerebellar changes are attributed to the cerebellum's role in motor output during locomotion, during motor learning, or in response to task-specific sensory input. It may be that subjects with relatively preserved spinocerebellar pathways are the ones that can respond to training, or it may be that the increased cerebellar changes result from a specific set of changes that first occur in the sensorimotor cortex and then subsequently affect cerebellar function.

The fMRI may serve not only as a reporter of neural plasticity but also as a predictor of functional outcomes for a rehabilitation technique by determining which regions of the human brain are critical for the relearning of walking in patients with SCI. This study reports different fMRI patterns of activation in patients who achieved functional over-ground ambulation following BWSTT compared to patients who did not. All the patients who underwent the same BWSTT demonstrated a cervical motor-incomplete SCI. The cerebellum was the only area that was activated preferentially in those patients who achieved functional over-ground ambulation. Used this way, fMRI may also provide insight into optimal durations of training to maximize the functional gains obtained with a task-specific rehabilitation strategy, such as BWSTT.

In conclusion, these findings suggest that intensive task-specific rehabilitative training such as that observed with BWSTT can promote supraspinal plasticity in the motor centers known to be involved in locomotion. Furthermore, this study provides preliminary evidence that in subjects with motor-incomplete SCI, improvement in over-ground locomotion appears to be accompanied by increased activation of the cerebellum. Although the Lokomat robotic orthosis was employed, changes observed may also occur with other forms of therapy. Although intriguing, we cannot definitively link the changes in brain activation to improved functional outcome. More patients must be evaluated to determine if the change in cerebellum activation during the course of a rehabilitation intervention such as BWSTT is requisite for locomotor improvement or if it can be used to predict maximal functional gains that can be achieved by a patient after SCI.

ACKNOWLEDGMENTS

This study was supported by the Western Rehabilitation Research Network under R24 HD39629 and Mobility Foundation Center at the University of Texas Southwestern Medical Center.

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