Increases in Corticospinal Tract Function by Treadmill Training After Incomplete Spinal Cord Injury

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INTRODUCTION

Animal and human studies have shown that after damage to the cerebral cortex, the recovery of motor function induced by intensive training is associated with structural and functional changes in the intrinsic circuitry of spared motor-related cortices (reviewed in Buonomano and Merzenich 1998; Nudo 2003). Such cortical reorganization is hypothesized to ultimately produce an expansion of and/or increase in the excitability of cortical networks supplying the affected muscles as revealed by imaging and transcranial magnetic stimulation (TMS) techniques (Karni et al. 1995; Levy et al. 2001; Liepert et al. 2000). After spinal cord injury (SCI) where only the downstream output of motor-related cortices are disrupted, evidence both for and against increases in the expansion and excitability of corticospinal pathways rostral to the lesion have been reported (Brouwer and Hopkins-Rosseel 1997; Levy et al. 1990; Topka et al. 1991). It has been postulated that the increased expansion and/or excitability of cortical networks innervating the unaffected muscles results from the exaggerated use of these muscles during motor compensation (Levy et al. 1990; Topka et al. 1991). From these initial observations in SCI and from the training studies described in the preceding text for stroke, we wished to study whether intensive training of muscles affected by SCI can increase the function of associated spared corticospinal pathways.

To examine the effects of training on spared corticospinal function directly, rather than from spontaneous motor recovery, we tested human subjects with injuries that were typically ≥1 yr and whose motor function had reached a plateau. To produce long-lasting improvements in leg motor function, subjects with incomplete SCI were trained 5 days/wk for 3–5 mo using treadmill therapy (Barbeau et al. 1987; Wernig et al. 1998), which consisted of body-weight support combined with manual assistance of leg movements over a motorized treadmill (Barbeau et al. 1987). Although our ultimate goal was to produce functional locomotor recovery and not to examine the efficacy of treadmill therapy per se, it remains unknown if treadmill training in chronic SCI is better than other approaches in restoring locomotor function (Dobkin and Havton 2004). We hypothesized that any form of locomotor training in humans would increase corticospinal tract function because the corticospinal tract, along with spinal circuits, provides a part of the drive to lower leg muscles during walking when examined in noninjured control subjects (Capaday 2002; Petersen et al. 2001).

To assess changes in corticospinal tract function from training, we measured motor-evoked potentials (MEPs) in response to incrementing levels of TMS over the leg area of the primary motor cortex. The resulting TMS-evoked recruitment curves recorded in muscles of the leg were typically well represented by a sigmoidal function (see Fig. 1) (see also Devanne et al. 1997). We measured changes in the threshold, slope, and maximum amplitude of the recruitment and sigmoidal curves (see METHODS) to determine if training affected the excitability, expansion, and/or functional connectivity of spared corticospinal networks activated by the TMS (Devanne et al. 1997; Ridding and Rothwell 1997). As this was a longitudinal study, we also compared the reproducibility of these parameters in nontrained SCI and noninjured controls to verify that any
Changes observed in the trained SCI group were indeed due to training.

The second purpose of our study was to examine if improvements in walking function from intensive treadmill training were related to increases in corticospinal tract function. In studies where quadrupedal animals are re-trained to walk after a complete SCI, the recovery of walking function has been postulated to be mediated by modifying the activation of locomotor and inhibitory networks intrinsic to the spinal cord (Edgerton et al. 2001; Ribotta et al. 2000; Tillakaratne et al. 2002). In contrast, in humans, attainment of independent walking from training only occurs in subjects having some preservation of voluntary leg movements (Dietz et al. 1994; Wernig and Muller 1992). Furthermore, functional gains made while walking on a treadmill in subjects that have gained a moderate walking capacity are transferable to overground walking. Thus in humans, training-induced improvements in walking function may not solely require increased activation of spinal locomotor networks that are entrained by locomotor-generated sensory inputs. Increases in the activation of spared descending pathways, such as the corticospinal tract, may also be necessary components to achieve attainment of functional independent walking. To test this, we examined if increases in locomotor recovery were correlated to increases in corticospinal tract function as assessed with TMS. Parts of this study have been presented in abstract form (Thomas and Gorassini 2004).

METHODS

Subjects

Ten subjects (8 male) with incomplete SCI aged 29–78 yr (54.4 ± 14.8; mean ± SD) volunteered with informed consent for this study (Table 1). Eight of them participated in TMS experiments both before and after receiving intensive treadmill training. Inclusion criteria for

<table>
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<tr>
<th>Code/ Sex</th>
<th>Age</th>
<th>Cause</th>
<th>Years Post Injury</th>
<th>Injury Level</th>
<th>Asia Score</th>
<th>Weeks Trained</th>
<th># of Sessions</th>
<th>Muscle Tested</th>
<th>Hot Spot (cm)</th>
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<td>C5/6</td>
<td>C</td>
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<td>78</td>
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<td>1.3–1.2</td>
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<td>5</td>
<td>L1</td>
<td>C</td>
<td>13</td>
<td>48</td>
<td>ITA</td>
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</tr>
<tr>
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<td>3</td>
<td>T5/9</td>
<td>D</td>
<td>19</td>
<td>60</td>
<td>rVL*</td>
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<td>0.8</td>
<td>T4/5</td>
<td>D</td>
<td>13</td>
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<td>T4/5</td>
<td>D</td>
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<td>D</td>
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<td>ITA</td>
<td>1.1–1.1</td>
</tr>
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</table>

In subjects where trauma was not the initial diagnosis, damage to the spinal cord was verified by magnetic resonance imaging (MRI). Subject 5M became paraplegic after surgical removal of a thoracic epidural abscess, subject 6M became paraplegic after removal of posterior elements of C4–T2, and subject 10F only had lesions in the spinal cord, with the brain and brain stem MRI being unremarkable. For hot spot location, the first coordinate denotes the lateral distance from vertex and the second coordinate denotes the posterior distance from vertex, i.e., 1, −1 for the right VL muscle of subject 1M signifies the hotspot was 1 cm left of and 1 cm posterior to vertex. NA, not appropriate; VE, viral encephalitis; TM, transverse myelitis; l, left; r, right. *denotes muscles where there was an increase in maximum motor-evoked potential (MEPmax) after training with more affected muscles in bilateral recordings marked in italics.
treadmill and TMS experiments were that subjects must have some ability to move one or more of their limb joints in both legs (ASIA C and D). Exclusion criteria were: damage to the nervous system other than the spinal cord; previous brain surgery; bone density that was \( \leq 30\% \) of age-matched, noninjured subjects; impaired mental capacity; history of epilepsy; spinal implants above C2; severe depression; and other medical contraindications to treadmill training (cardiovascular problems, back or joint injury, arthritis, pulmonary disorders, history of deep vein thrombosis, etc.). Motor function scores (see Clinical measures) assessed between the time of initial screening and immediately before the start of training (typically a 2-mo period) did not change indicating that all subjects were not in a process of spontaneous motor recovery before the start of treadmill training. Five noninjured control subjects [3 of them male, 21–36 yr (26 \( \pm \) 6)] and six nontrained SCI subjects, four of whom were subsequently trained (subjects 3M, 6M, 7M, 8F, see Table 1) were also tested for day-to-day variability of the MEPs. Ethics approval for this study was obtained from the Human Ethics Research Committee at the University of Alberta.

Treadmill training

Eight of the 10 SCI subjects were asked to take part in five training sessions/week. On average, subjects participated in 4.1 \( \pm \) 0.76 sessions per week for an average of 16.6 \( \pm \) 4.4 wk (see Table 1 for individual training times and sessions completed). Each training session was 1 h in duration and consisted of body-weight support combined with manual assistance of leg movements while the subject walked on a motorized treadmill. Depending on the need, one or two people were positioned at the lower limb to provide stepping assistance by lifting the foot through swing, flexing the knee at the start of swing, and/or stabilizing the leg during stance. A bungee cord tied to the harness and overhead support frame was sometimes used to help stabilize the subject’s posture. The base of support, weight shift between the two legs, step length, postural alignment, hip extension at the start of swing, and foot contact during stance (heel to toe) were all monitored. Subjects were encouraged to arm swing when possible (1 or 2) and horizontal bars positioned at chest level were used to aid in balance control only. Subjects walked at a slow pace (=1.5 km/h or 1 mph), enabling them to concentrate on voluntarily activating their muscles during walking. Rests were taken when needed but subjects were encouraged to walk/rest at 10-min intervals. When the physical therapist noticed improvements in cardiovascular tolerance, proper limb kinematics throughout the step cycle, weight transition between limbs and upright trunk alignment, the amount of body weight support and/or stepping assistance were gradually decreased. On average, body weight support decreased from 44.3 \( \pm \) 25.2% at the start of training to 13.4 \( \pm \) 18.1% at the end of training. Subjects were not allowed to wear lower-extremity orthoses while training. In three subjects (6M, 7M, 8F), training of overground walking after a treadmill session was also performed once or twice a week during the last 1 or 2 mo of training. Training was stopped when improvements in walking ability, as assessed by the WISCI II score, how much distance a subject could walk in 6 min, and the time it takes to walk 10 m, remained constant over a 4-wk period.

TMS

TMS was produced by a Magstim Model 200 stimulator (Magstim) and a large double-cone coil (P/N 9902–00) having an inside diameter of 96 mm and an outside diameter of 125 mm for each individual coil. MEPs were evoked in the tibialis anterior (TA) muscle; however, in two subjects (1M and 4M) MEPs were evoked in the vastus lateralis (VL) muscle because it was not possible to maintain a constant background contraction of TA (see following text). To determine the optimal location on the scalp to elicit a MEP in either the TA or VL muscle, vertex (Cz with 0 mediolateral and 0 anteroposterior coordinates) was first marked on the scalp and a transparent grid with 1 \( \times \) 1 cm markings was centered over the vertex. Different locations on the grid, usually centered around 1 cm lateral and 1 cm posterior to Cz (1, \(-1\)), were stimulated at an intensity that was \( \sim \)1.2 times the motor threshold. The location where the largest and most consistent MEP was elicited, i.e., hot spot, was marked on the scalp and the mid-point of the coil was positioned over this spot to obtain a TMS recruitment curve (described in the following text). When possible, a hot spot was identified over both the right and left motor cortices (see Table 1). The position of the coil was maintained flush with the subject’s head by the experimenter and the position and orientation were periodically checked throughout the experiment to ensure that the handle was perpendicular to the scalp and that the grid did not move from its original location.

EMG recording

Surface EMG activity was recorded from leg muscles on the right and left side of the body, including the TA and soleus (SOL) muscles of the TA and hamstrings (HAM) muscles. The skin surface over each muscle was shaved, cleaned with alcohol and allowed to dry. Two disposable silver/silver chloride-recording electrodes (Kendall Soft –E H59P) were placed 1.5 cm apart over the prepared area. EMG signals were led to an isolated preamplifier/amplifier (Octopus, Bortec Technologies, Calgary, AB) with a band-pass of 10–1,000 Hz, and the signal was amplified between 1,000 and 5,000 times. The EMG signal was digitized with a 5-kHz sampling rate using AxoScope hardware and software (DigiData 1200 Series, Axon Instruments, Union City, CA), and displayed on a personal computer.

Experimental protocol (TMS)

For each pretraining experiment, subjects were instructed to maintain a background voluntary contraction that was \( \sim \)10% of their maximum (MVC) in either the TA or the VL muscle. MEP responses were measured during muscle activation to control for both cortical and motoneuron pool excitability and to ensure that changes in response to TMS were not simply a result of differences in sub-threshold activation of neurons (Ridding and Rothwell 1995). To help subjects maintain a 10% MVC, the surface EMG signal was rectified, low-pass filtered (3 Hz), and displayed on an oscilloscope with a fast time scale. The subject was asked to contract their leg muscle until the rectified EMG signal reached a horizontal line on the oscilloscope that corresponded to \( \sim \)10% of MVC. To produce a TMS recruitment curve (Fig. 1), the applied stimulation intensity was increased, from below motor threshold to maximum MEP (MEP\(_{\text{max}}\)), in increments of 5 or 10% of the maximum stimulator output (MSO). Typically, stimulation intensities ranged from 30 to 80% of MSO, with four stimuli given at each intensity every 5–6 s. Brief rest periods were given between the different stimulation intensities. MEPs were collected from both sides of the body unless the patient could not maintain a steady background contraction in the target muscle (e.g., subjects 2M, 3M, and 4M, Table 1). The identical experimental protocol was used posttraining. Subjects did not train on the day of a TMS experiment, and all subjects were tested within 1 wk before or after training was concluded. The location of the hot spot was re-identified and typically similar coordinates were used (see Table 1). The maximum amplitude of the rectified and smoothed EMG signal during a MVC was also re-measured after training. Care was taken to place the surface EMG electrodes in the same location, and similar background EMG activity was maintained to ensure that larger background EMG was not used on the posttraining recording day. For example, when a subject’s MVC increased posttraining, background contractions \(<\)10% MVC were needed to match levels reached during pretraining testing.

Similar procedures as described for the trained SCI subjects were used with uninjured and nontrained SCI control subjects where
recruitment curves were recorded on different experimental days. A nontrained SCI group was included to determine if the amount of day-to-day variability of recruitment curves was larger in subjects with SCI given that maintaining a constant background EMG would be more difficult for these subjects. Specifically, the absolute background EMG of the target muscle and the location of the hot spot were the same on different recording days. Recording days were separated by 1 wk in both noninjured and nontrained SCI subjects except for two noninjured subjects that were tested 2 and 9 mo apart. The noninjured controls were younger than the SCI trained group (see Subjects above). Because age does not affect the threshold, slope or \( M_{\text{EP}}^\text{max} \) values of TMS recruitment curves (although peak slope and \( M_{\text{EP}}^\text{max} \) of the recruitment curve occurs at lower stimulation intensities in younger subjects), we felt that age would not appreciably affect the day-to-day variability in TMS recruitment curves (Pitcher et al. 2003). Both noninjured and non-SCI subjects were instructed to not engage in motor activities that were outside of their normal, weekly routine. All subjects were re-tested at the same time of day, either mid-morning or early afternoon.

**Data analysis:** recruitment curves

Axoscope files were imported into Matlab 6.5 (The Mathworks, Natick, MA) for off-line analysis. Custom Matlab software was used to obtain a peak-to-peak value for the MEP response by setting a time window around the MEP and calculating the maximum and minimum amplitude for the unrectified EMG signal in this window. At a given stimulation intensity, the four peak-to-peak MEPs were measured and then averaged together. The averaged MEP response was plotted against the corresponding stimulation intensity as per Capaday et al. (1999) to produce a recruitment curve (Fig. 1B). A four-parameter sigmoid function (Boltzman) was fit to this recruitment curve (see also Knash et al. 2003) that included a parameter for background EMG activity given that there was a measurable peak-to-peak EMG response when no MEP was present. Four specific parameters of the recruitment and sigmoid curves were measured: \( M_{\text{EP}}^\text{max} \times [r] \), which was the largest MEP evoked in the facilitated muscle and typically occurred at the largest stimulation intensities; \( M_{\text{EP} \text{thres}}^\text{a}, \) which was measured from the sigmoid curve at the stimulation intensity that produced a half-maximum response in the before-training condition (Carroll et al. 2001; Knash et al. 2003); \( M_{\text{EP} \text{thres}}^\text{b} \), which was the stimulation intensity that produces 5% of maximum of the sigmoid curve (similar to Carroll et al. 2001); and the slope of the steepest region of the sigmoid curve (measured near \( M_{\text{EP} \text{thres}}^\text{b} \)) (Devanne et al. 1997). In addition to measuring the peak-to-peak values of the MEP, the mean rectified value of EMG over the period of measurement of the MEP was also calculated. To calculate the average background EMG activity at each stimulation intensity, the mean amplitude of the rectified EMG was calculated over a 27-ms window prior to the stimulation with the mean of all points for a given recruitment curve marked by a horizontal line (see Fig. 1B, bottom).

**Silent period**

The silent period, a cessation of background EMG activity after the MEP, was calculated at each stimulation intensity by measuring the time from the end of the MEP to the earliest re-emergence of background EMG in at least two of the four TMS trials that best showed a clear silent period (see horizontal lines in Fig. 1A) (Garvey et al. 2001). The duration of the silent period was plotted against the corresponding stimulation intensity to produce a silent-period recruitment curve (e.g., Fig. 6A). The threshold of the silent period was measured as the lowest stimulation intensity where a cessation of background EMG activity, lasting for \( \approx 20 \) ms, could be observed in at least two of the four TMS trials. The duration of the silent period measured at \( M_{\text{EP} \text{max}} \) and the threshold of the silent period were compared before and after training using paired Student’s \( t \)-test (see following text).

**Locomotor EMG and clinical motor measurements**

Surface EMG activity from the TA, SOL, VL, and HAM muscles and ankle and knee joint angle trajectories (via goniometry, Biometrics) were measured both before and after training as subjects walked on a motorized treadmill (5-kHz sample rate). Using custom Matlab software, EMG signals were rectified and low-pass filtered (100 Hz), and \( \approx 25 \) steps were averaged together using joint angle trajectories to align the averages. The peak amplitude of the locomotor EMG burst, minus background noise, was compared before and after training. In addition, the distance a subject could walk in a 6-min period and the time it took to walk 10 m (both measured at preferred walking speeds) were measured along with a qualitative locomotor score, the WISCI II (Ditunno and Ditunno 2001), which is a 21-point scale that measures the degree of assistance and gait aids required to walk 10 m. Each was measured both before and after training by the physical therapist performing the treadmill training. An 11-point manual muscle strength score was measured for the ankle dorsiflexors or knee extensors before and after training, where: 0 = no palpable or visible muscle contraction, 1 = muscle contraction palpable or visible, 2 = complete range of movement with gravity eliminated, 3 = complete range of movement against gravity, 4 = complete range of movement with moderate resistance, 5 = complete range of movement with maximum resistance. Sub-scores were given between the 1 and 4 scales if subjects were able to partially perform a given movement, e.g., 2+ = <50% initiation of motion against gravity and was given a value of 2.3. Along with MVC measurements, the maximum evoked response to direct nerve stimulation (\( M_{\text{max}} \)) was tested in the TA or SOL muscle by applying incrementing levels of percutaneous stimulation (1-ms pulse width) over the common peroneal or tibial nerve until a maximal M-wave response was produced. The average peak-to-peak amplitude of three \( M_{\text{max}} \) responses was compared both before and after training.

**Statistical analyses**

Paired Student’s \( t \)-test were used to compare differences between the various parameters of the recruitment/sigmoid curves (\( M_{\text{EP} \text{max}} \), \( M_{\text{EP} \text{thres}} \), slope, and silent period) before and after training in SCI subjects using SigmaPlot 8 software. Similarly, paired Student’s \( t \)-test were used to compare differences between muscle strength scores, percent changes in MVC, \( M_{\text{max}} \) distance walked in 6 min, time to walk 10 m and peak locomotor EMG. A Wilcoxon signed-rank test was used to compare ordinal WISCI II scores before and after training using SPSS11 software. To compare the changes in recruitment/sigmoid curve parameters between the different recording days in trained SCI, nontrained SCI and noninjured controls, a one-way ANOVA for repeated measures was used with post hoc \( t \)-test analysis (Bonferroni-corrected for multiple corrections) using SPSS11 software. The percentage increase in \( M_{\text{EP} \text{max}} \) was correlated with changes in WISCI II score, distance walked in 6 min and peak locomotor EMG activity using a Pearson’s \((r)\) correlation coefficient. For all tests, a \( P \) value of \(<0.05\) was used to indicate statistical significance. All values are expressed in terms of means \( \pm \) SE unless otherwise stated.

**RESULTS**

**Training-induced changes in TMS recruitment curves:** \( M_{\text{EP} \text{max}} \) and \( M_{\text{EP} \text{thres}} \)

Before training, recruitment curves obtained from plotting the mean peak-to-peak MEP against the corresponding TMS intensity were well fit by a sigmoid function in both TA and
VL muscles as a large percentage of the variance in the MEP ($R^2$) was accounted for by the sigmoid curve ($R^2 = 0.82$). After several months of intensive treadmill training, the size of the MEP increased as reflected by a vertical shift of the recruitment curves (Fig. 2, median $R^2 = 0.88$). Various patterns of recruitment shift occurred and ranged from cases where MEPs were mainly enhanced at high levels of stimulation intensity (as shown for the TA muscle in Fig. 2) to cases where MEPs were enhanced starting at low stimulation intensities (as shown for both VL muscles in Fig. 2). Note that the changes in recruitment curves after training occurred even though subjects maintained similar background EMG activity compared with before training trials (see Fig. 2, bottom).

In the eight trained subjects, MEP responses were measured in 13 muscles with 5 of these subjects being tested on both legs. Of the eight subjects tested, seven demonstrated an appreciable training-induced increase in the maximum MEP ($\text{MEP}_{\text{max}}$) in at least one of their leg muscles, with two of the five subjects tested bilaterally having increases in both leg muscles (9/13 muscles, Table 1). When comparing across all 13 muscles from the eight subjects, $\text{MEP}_{\text{max}}$ increased from a mean of 729.0 ± 78.3 µV before training to a mean of 1,000.9 ± 84.3 µV after training (Fig. 3A, left, significantly different) when measured at similar levels of background EMG (Fig. 3A, right). When comparing the percentage increase of $\text{MEP}_{\text{max}}$ in each muscle before and after training to normalize for differences in absolute $\text{MEP}_{\text{max}}$ size across subjects [(after $\text{MEP}_{\text{max}}$ – before $\text{MEP}_{\text{max}}$)/before $\text{MEP}_{\text{max}}$ × 100%], there was an average percent increase of 46.3 ± 12.3% across all muscles (Fig. 3B, left, significantly different from 0).

We also compared MEPs that were evoked during mid-range stimulation intensities, i.e., $\text{MEP}_{\text{h}}$, which was measured at the stimulation intensity that produced half the maximum response before training (see solid vertical lines in Fig. 2). Similar to $\text{MEP}_{\text{max}}$, the mean $\text{MEP}_{\text{h}}$ in all 13 muscles increased from 428.5 ± 41.5 before training to 571.4 ± 65.7 µV after training (Fig. 3C, left, $P = 0.07$, not significantly different) when

![FIG. 2. Representative recruitment curves from 3 different subjects before (●, —) and after (○, - - -) treadmill training. Top: recruitment curves from the TA (subject 5M, left) and VL muscles (subject 4M, middle; subject 1M, right). In all 3 examples, the recruitment curves after training rested above the recruitment curves before training, especially at intermediate and high stimulation intensities. The slope of the steep portion of the sigmoid line fit to the recruitment curve also increased after training although $\text{MEP}_{\text{thresh}}$ did not change in most cases. Bottom: the mean background EMG after training (●) was similar to the background EMG before training (—). Data points represent trial means ± SD.](http://jn.physiology.org/)

![FIG. 3. Mean MEP and threshold responses before (●) and after (○) treadmill training for all 13 muscles tested. Mean peak-to-peak $\text{MEP}_{\text{max}}$ (A, left) and corresponding mean percentage increase of $\text{MEP}_{\text{max}}$ (B, left) was larger after training when measured at similar mean background EMG (right bars in A show mean background EMG at $\text{MEP}_{\text{max}}$, mean percentage change in B). Likewise, $\text{MEP}_{\text{h}}$ increased after training (C, left) and the mean percentage increase in $\text{MEP}_{\text{h}}$ was significant (D, left) at comparable background EMG (right bars in C show mean background EMG for entire recruitment curve, mean percentage change in D). $\text{MEP}_{\text{thresh}}$ did not change after training (left bars in E, average change in F), whereas the slope of the sigmoid curve did increase after training (right bars in E, average percentage increase in F). Bars represent group means ± SE. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$](http://jn.physiology.org/)}
compared at similar levels of background EMG (Fig. 3C, right). Correspondingly, the average percentage increase in MEP\textsubscript{p} was 45.4 ± 20.3\% (Fig. 3 D, left, significantly different from 0).

Comparable training-induced increases in MEP responses were also observed when measuring the mean rectified values of the MEP as opposed to measuring the peak-to-peak MEP. For example, the mean rectified MEP\textsubscript{\text{max}} increased from 61.1 ± 8.3 \mu\text{V} before training to 95.0 ± 11.7 \mu\text{V} after training (significantly different), a 55.7\% increase.

Training-induced changes in TMS recruitment curves: slope and MEP\textsubscript{thresh}

On average, the slope region of the sigmoid fit to the recruitment curve was steeper after training compared with before as shown for all muscles in Fig. 2. When compared across all muscles, the average slope of the sigmoid increased from 41.2 ± 5.7 to 65.3 ± 6.0 \mu\text{V}/MSO (significantly different, Fig. 3E, right), suggesting an increase in the excitability and/or expansion of corticospinal networks after training (Ridding and Rothwell 1997). Correspondingly, the average percent increase in peak slope was 23.9 ± 7.1\% (Fig. 3F, right, significantly different from 0). Changes in the threshold to evoke a MEP response (MEP\text{\textsubscript{\text{thresh}}}), a measure of the excitability of the lowest-threshold corticospinal tract networks, were quite variable among subjects. When compared across all muscles, MEP\text{\textsubscript{\text{thresh}}} (see METHODS for definition) did not change after training as shown for the TA and VL muscles in Fig. 2 (left and middle). The mean MEP\text{\textsubscript{\text{thresh}}} across all muscles was 48.7 ± 3.9\% MSO before training and 47.2 ± 3.9\% MSO after training (Fig. 3E, left, not significantly different) and corresponded to an average absolute decrease in MEP\text{\textsubscript{\text{thresh}}} of only −2.9 ± 2.2\% MSO (Fig. 3F, left, not significantly different from 0).

In five subjects, TMS measurements from muscles on different sides of the body in same subject were included in the overall averages because we considered them to be relatively independent measures given that they were produced from two separate corticospinal pathways that need not have been under simultaneous control during locomotor training. In fact, in the majority of subjects from which bilateral recordings were made (3/5 subjects), changes in MEP responses from the left corticospinal tract were different from the changes measured from the right corticospinal tract. None-the-less, when comparing the various recruitment curve parameters (MEP\text{\textsubscript{\text{max}}}, MEP\text{\textsubscript{b}}, MEP\text{\textsubscript{\text{thresh}}}, and slope) in only eight muscles from each of the eight subjects (grouped by either right or left muscles from subjects with bilateral recordings), differences before and after training were still statistically significant for MEP\text{\textsubscript{\text{max}}} and slope, similar to that shown for the 13 muscle averages.

Latencies at MEP\textsubscript{\text{thresh}} and MEP\textsubscript{\text{max}}

The mean latency at which a notable (=50 \mu\text{V}) MEP response was visible in the raw EMG signal (i.e., near MEP\text{\textsubscript{\text{thresh}}}) was similar to the latency of the MEP evoked at MEP\text{\textsubscript{\text{max}}} both before (39.4 ± 1.1 vs. 38.6 ± 2.2 ms) and after training (37.8 ± 1.7 vs. 38.2 ± 2.1 ms, P > 0.66). Moreover, there were no statistical differences between corresponding threshold and MEP\text{\textsubscript{\text{max}}} latencies before and after training (P > 0.20).

Changes in antagonist MEP responses

When eliciting MEP responses in the facilitated target muscles (TA or VL), MEP responses were often evoked in the corresponding antagonist muscle, i.e., SOL or HAM, respectively, even though these muscles were electrically silent just prior to the TMS. Similar to the target muscles, there was also a training-induced increase in MEP\text{\textsubscript{\text{max}}} of the antagonist muscles as shown for the SOL muscle in Fig. 4. Interestingly, in the nine target muscles that demonstrated a training-induced increase in MEP\text{\textsubscript{\text{max}}}, there was also an associated posttraining increase of 107.3\% in MEP\text{\textsubscript{\text{max}}} of the corresponding antagonist muscle when averaged across all nine muscles. However, the absolute MEP values in antagonist muscles were much smaller than in target muscles, increasing from 102.6 ± 29.7\% before training to 212.7 ± 37.5 \mu\text{V} after training (significantly different). In the four target muscles that did not show an increase in MEP\text{\textsubscript{\text{max}}} the average MEP\text{\textsubscript{\text{max}}} of the corresponding antagonist muscles also did not increase after training (from 145 ± 62.3 to 123.0 ± 50.6 \mu\text{V}, not significantly different). The parallel changes in MEP\text{\textsubscript{\text{max}}} of target and antagonist muscles after training suggest that there was a general increase in the connectivity of corticospinal inputs to muscles of the leg.

Maximum voluntary contractions and M-waves

After training, the peak of the rectified and smoothed EMG activity of the target muscles reached during a maximum voluntary contraction, or MVC, increased, on average, by 16.0\% from 164.3 ± 19.0 \mu\text{V} before training to 191 ± 24.7 \mu\text{V} after training (statistically different from 0). Likewise, the manual muscle strength score (see METHODS) increased from 3.1 ± 0.3 before training to 4.0 ± 0.3 after training (significantly different, P < 0.0002). In contrast, the maximum evoked response from direct motor axon stimulation, or M\text{\textsubscript{\text{max}}} did not change when tested in the SOL (n = 5) and TA (n = 2) muscles (1.2 ± 0.4 mV before vs. 1.3 ± 0.5 mV after, peak-to-peak M\text{\textsubscript{\text{max}}} values, tested in 7 subjects, not significantly different), suggesting that training-induced changes in MEP responses were of central, and not muscle, origin. Moreover, stable M\text{\textsubscript{\text{max}}} responses before and after training verifies that comparison of raw EMG values (e.g., peak-to-peak MEP or mean rectified MEP) was valid.

FIG. 4. Antagonist MEPs (4 superimposed raw EMG traces) of the soleus (SOL) muscle (bottom) to TMS while the subject (7M) produced a background contraction of the target (agonist) tibialis anterior (TA) muscle (top). Before training (left) MEPs were not evoked in the electrically silent SOL muscle. After training (right), the MEP in the facilitated TA muscle increased and a MEP emerged in the SOL muscle with a similar latency to that of the TA muscle (40 ms TA vs. 41 ms SOL). ↑, the time of the 80\% maximum stimulator output (MSO) stimulation.
Reproducibility of MEP measurements

$\text{MEP}_{\text{max}}$ AND $\text{MEP}_{\text{th}}$. To ensure that the changes in recruitment curves observed after training were not simply due to day-to-day variability in the TMS-evoked MEP responses, experiments in noninjured control and nontrained SCI subjects, i.e., subjects who should be neurologically stable, were performed on different experimental days. Because noninjured control subjects had much higher MEPs than SCI subjects, we compared the percentage change [(experiment 2 − experiment 1)/experiment 1 × 100%] in $\text{MEP}_{\text{max}}$ and $\text{MEP}_{\text{th}}$ between the different groups. The mean percentage change in $\text{MEP}_{\text{max}}$ from day-to-day in noninjured control ($-1.2 \pm 1.6\%$) and nontrained SCI subjects ($4.2 \pm 9.2\%$) was significantly smaller than the percentage increase measured in trained SCI subjects ($46.3 \pm 12.3\%$, Fig. 5A, see also Fig. 3B, 1-way ANOVA: $F = 5.29$, df = 2, 24, $P < 0.05$). Likewise, the mean percent increase in $\text{MEP}_{\text{th}}$ was greater for SCI trained ($45.4 \pm 20.2\%$, Fig. 5B) compared with noninjured ($7.0 \pm 12.0\%$, $P = 0.12$) and nontrained SCI subjects ($-4.5 \pm 15.8\%$, $P = 0.38$, $F = 2.14$, df = 2, 24), although the increase in $\text{MEP}_{\text{th}}$ did not reach significance.

SLOPE OF Sigmoid AND $\text{MEP}_{\text{th}}$. The mean percent increase in the slope of the sigmoid fit to the recruitment curve in trained SCI subjects ($23.9 \pm 7.1\%$, Fig. 5D) was statistically greater compared with noninjured ($-0.8 \pm 9.1\%$) and nontrained SCI subjects ($6.6 \pm 2.4\%$, $F = 4.74$, df = 2, 24, $P < 0.05$). Mean changes in the absolute $\text{MEP}_{\text{th}}$ between different experiment days in noninjured ($1.8 \pm 1.3\%$ MSO) and nontrained SCI subjects ($4.4 \pm 2.6\%$ MSO) were not statistically different to the mean decrease in $\text{MEP}_{\text{th}}$ in trained SCI subjects ($-2.9 \pm 2.2\%$ MSO, $F = 3.04$, df = 2, 23, $P > 0.06$, Fig. 5C).

Training-induced changes in silent period EMG

Similar to the MEP responses, the duration of the silent period increased after training, as shown for subject 6M in Fig. 6A. It was expected that the larger MEP responses after training would also be associated with longer silent periods due to concomitant increases in activation of inhibitory spinal interneurons and/or motoneuron refractory periods (Trompetto et al. 2001). However, silent periods lasting beyond 100 ms, where influences from spinal mechanisms are relatively small (Fuhr et al. 1991; Ikeda et al. 2000), still showed training-induced effects. For example, the average silent period measured at $\text{MEP}_{\text{max}}$ increased from 130.1 ± 19.9 ms before training to 178.4 ± 27.9 ms after training (Fig. 6B, left, significantly different). In addition, the threshold to evoke a silent period (see METHODS) decreased from 49.1 ± 3.2% MSO to 41.8 ± 2.7% MSO (Fig. 6B, right, significantly different), with the incidence of a subthreshold silent period increasing from 42% of all muscles tested before training to 75% after training.

Correlation between changes in corticospinal tract connectivity and locomotor function

All but one subject (3M) demonstrated improvements in walking function after training as reflected in the increase in WISCI II scores from a mean of 6.4 ± 2.2 before training to a
mean of 9.8 ± 2.4 after training (Fig. 7A, P = 0.027, Wilcoxon signed-ranks test). Interestingly, subject 3M also did not exhibit an appreciable (>20%) increase in MEP$_{\text{max}}$ in response to training. Thus we wanted to examine if there was a correlation between increases in MEP$_{\text{max}}$ and increases in locomotor function gained from training. We found that there was a significant correlation within patients between the percent increase in MEP$_{\text{max}}$ and the absolute increase in WISCI II score (Fig. 7B, $r = 0.71$, $r$ = correlation coefficient). Subject 8F, who had a high WISCI II score before training (17, the upper end of the scale), was excluded from the analysis because we have found previously that such subjects can improve in walking function from training (endurance, speed, etc.) but tend not to advance in their WISCI II scores (personal observations) Similar to that shown for the WISCI II scores, the distance that a subject could walk in 6 min increased significantly from 34.2 ± 17.7 m before training to 167.6 ± 51.9 m after training (Fig. 7C) and the peak locomotor EMG activity reached during walking on a treadmill increased from 82.4 ± 25.6 to 137.1 ± 10.9 μV (Fig. 7E, not significant at $P = 0.06$). When examining overground walking speed in the four subjects that were able to walk before training (2M, 6M, 7M, and 8F), the average time it took to walk 10 m was lower after training (18.8 ± 6.4 s) compared with before (62.6 ± 40.5 s), resulting in an average percentage decrease of 42% (significantly different from zero). Both the increase in distance walked and the increase in peak locomotor EMG correlated significantly to the percent increase in MEP$_{\text{max}}$ ($r = 0.90$ and 0.79, respectively, Fig. 7, D and F). There was no significant correlation between the percentage increase in MEP$_{\text{max}}$ and the age of the injury ($r = 0.47$).

In two subjects, 4M and 5M, it was possible to re-measure recruitment curves 2.5 yr after training. Both subjects maintained the gains in walking function that were obtained from treadmill training. As shown in Fig. 8, the recruitment curves recorded a few years after training (●) remained well above the recruitment curves measured before training (○) and were similar to the recruitment curves recorded immediately after training (◇).

**DISCUSSION**

This is the first study to examine the effects of long-term (3–5 mo) motor training on spared corticospinal function in subjects with incomplete SCI. We found that intensive treadmill training, and in some cases additional overground training, produced a generalized increase in the connectivity of spared corticospinal pathways, as noted by increases in MEP$_{\text{max}}$ of both target (TA and VL) and antagonist (SOL and HAM) muscles. Training-induced increases in the excitability and/or expansion of corticospinal networks were also suggested by increases in the slope of the sigmoid function fit to the recruitment curve. However, training did not produce increases in the excitability of the lowest-threshold corticospi-
nal tract pathways, as MEP\textsubscript{thresh} was not changed posttraining. We also observed that the duration of the silent period increased after training, even for silent periods lasting >100 ms, where beyond this point, silent periods are mainly produced by cortical mechanisms. One of the striking results from this study was the strong relationship between the percent increase in MEP\textsubscript{max} (corticospinal connectivity) and the improvement in walking function achieved as a result of daily intensive training, suggesting that recovery of walking was, in part, mediated by the corticospinal tract. Finally, when measured 2.5 yr after training, increases in corticospinal tract function were maintained in subjects that continued to use the new locomotor abilities gained from intensive training.

Changes in MEP responses due to motor training

The changes in MEP responses recorded months after the onset of training could have resulted from day-to-day variability in MEP recordings known to be associated with TMS (summarized in Carroll et al. 2001). However, the fact that percent increases in MEP\textsubscript{max} and the slope of the sigmoid curve were statistically different from the percent changes measured on different recording days in noninjured control and nontrained SCI subjects strongly suggests that the increases in corticospinal tract function were indeed a result of intensive daily training. Although the control subjects were re-tested at shorter time intervals compared with the trained SCI subjects (1 wk vs. 4 mo), the day-to-day variability in TMS parameters in two noninjured control subjects that were tested 2 and 9 mo apart were not different from noninjured controls tested at the 1-wk interval (see Fig. 5 legend for values). Likewise, we would expect that nontrained SCI subjects that had long-standing injuries and/or stable clinical motor scores before training to not demonstrate marked changes in TMS parameters over time if they were not trained. In fact, in SCI subjects that were tested on two separate recording days before training, differences in MEP\textsubscript{max} and slope were statistically greater after training than before but not between the different pretraining recording days. Values of MEP\textsubscript{thresh} proved to be more variable across the different recording days, but as a whole, threshold did not change after training. An unchanging MEP\textsubscript{thresh} suggests that the effective stimulus to the motor cortex from TMS did not change appreciably before and after training, so the observed increases in MEP and silent period values were truly a result of training-induced changes in corticospinal tract function rather than a result of greater stimulation currents reaching the cortex.

The highly reproducible responses in noninjured controls and nontrained SCI subjects may have been due to the fact that we used a large stimulating coil, which produces MEP responses that are not sensitive to small changes in coil position and orientation (see also Carroll et al. 2001). As long as subjects maintained a constant level of background EMG facilitation, MEP responses measured on different recording days were very stable when subjects were not being trained. In contrast, motor maps produced by stimulating a 6 × 6-cm grid over the leg region of the primary motor cortex were very variable from day to day in both noninjured and SCI subjects as it was more difficult to maintain a constant level of background EMG activity throughout the many stimulation trials required to produce a motor map (unpublished results) (see also Wolf et al. 2004).

Increases in MEP responses were also observed after training in electrically quiet antagonist muscles. It is possible that increases in antagonist MEP responses may have been due to systematic increases in the subthreshold depolarization of the respective motoneuron pools or cortical neurons. For example, imagined motor movements that have the potential to increase the subthreshold level of activation of cortical and spinal neurons have been shown to facilitate MEP responses in lower limb muscles at rest (Tremblay et al. 2001). However, systematic increases in the subthreshold activation of antagonist cortical or spinal neurons after training are unlikely for several reasons. First, the background level of EMG activation in the target (agonist) muscles was the same or even lower after training; thus one would expect that the subthreshold level of activation of cortical and neuron pools of the antagonist muscles would also be about the same or lower. Second, training tended to decrease the amount of co-contraction between flexor and extensor muscles during walking (unpublished results) so that co-activation of antagonist muscles during a steady contraction of a target muscle should also be reduced after training. Finally, when MEP\textsubscript{max} increased in a target muscle after training, it also increased in the corresponding antagonist muscle; likewise, when MEP\textsubscript{max} remained constant or slightly

![FIG. 8. Recruitment curves recorded in subjects 4M (A) and 5M (B) 2.5 yr after receiving treadmill training (C). The follow-up recruitment curves remained above the recruitment curves recorded before training (○) and were similar to the recruitment curves recorded immediately after training (×). Data points represent trial means ± SD.](http://jn.physiology.org/ downloaded from on October 29, 2017)
decreased in a target muscle after training, its response in the antagonist muscle followed suit. Thus the corticospinal tract supplying antagonist muscles followed the general excitability changes of the corticospinal tract supplying agonist muscles where the level of excitation was controlled for both before and after training.

The increases in TMS responses observed posttraining could potentially arise from a transient increase in corticospinal tract excitability after a single bout of walking in the SCI subjects and thus confound our interpretation of the data, especially in subjects that walked into the lab posttraining but wheeled in pretraining. However, this was only the case in two of the eight SCI subjects (6M and 7M), and these subjects did not demonstrate increases in TMS responses that were greater than the other subjects using the same modality of transport to the experiment. Moreover, subjects were not trained on the day of the TMS experiments to ensure that we were not examining transient effects from a single bout of training.

Origin of changes in corticospinal tract function

Given that the evoked responses from direct nerve stimulation (e.g., \( M_{\text{max}} \)) did not change after training, the increases in TMS-evoked MEPs, and thus increases in corticospinal tract function, were presumably central in origin. However, by only using TMS, it is not possible to determine if the observed increases in spared corticospinal tract function were cortical or spinal in origin (or both). Studies employing short-term motor skill training in noninjured controls have demonstrated that training-induced increases in TMS-evoked MEPs are cortical in origin because MEPs elicited by transcranial electrical stimulation, which mainly activates the axon hillock of corticospinal fibers, are not affected by training (Perez et al. 2004). Likewise, early reports of imaging studies in incomplete SCI subjects reveal treadmill training can induce reorganization in cortical leg representations (Dobkin 2000). In line with these two studies, we found that silent periods lasting >100 ms (as occurred at \( M_{\text{max}} \)) increased even further in duration after training. Because the silent period beyond 100 ms is mainly cortically mediated (Fuhr et al. 1991; Ikeda et al. 2000), long-term motor training likely affected the excitability of cortical tissue that was being activated by the TMS. In addition, we did not observe increases in the amplitude of H-reflexes evoked in either the SOL or TA muscles after training (M. Gorassini and J. Yang, unpublished observations; see also Schneider and Capaday 2003; Trimble et al. 2001), suggesting that the excitability of spinal circuits did not change appreciably (although different spinal networks may be activated by TMS vs. H-reflexes). Finally, the lack of change in MEP\(_{\text{thresh}}\) and the concomitant increase in slope of the sigmoid curve is consistent with an expansion of cortical sites activating the muscles of the lower leg as a result of training (Perez et al. 2004; Ridding and Rothwell 1997).

TMS can activate pyramidal axons directly (D waves), especially at high stimulation intensities, and indirectly via interneurons (I waves), especially at low stimulation intensities (Di Lazzaro et al. 2001; Edgley et al. 1997). If MEP responses at high stimulation intensities were activated predominantly by D waves, then increases in \( M_{\text{max}} \) from training would most likely result from increases in spinal excitability. However, the latency of the MEP at threshold (low stimulation intensities) was similar to the latency at \( M_{\text{max}} \) (high stimulation intensities), indicating that we were not consistently evoking D waves at high levels of stimulation intensity. Thus increases in \( M_{\text{max}} \) after training were perhaps a result of increased I-wave activation as a result of increased excitability of intrinsic cortical networks or their inputs (Ridding and Rothwell 1995). In line with this, MEPs that were activated during mid-range TMS intensities (at \( M_{\text{p}} \)), where there is most likely to be I-wave activation, were also increased after training and provide supportive evidence for the excitability/expansion of cortical networks. Regardless of the location, the important finding is that the function of the spared corticospinal tract can be enhanced after SCI after several months of intensive training, even for injuries that have occurred many years before training (see Table 1). Such increases in corticospinal tract function appear to be long-lasting when the trained locomotor function is maintained; however, it remains to be tested if corticospinal tract function decreases when locomotor function cannot be maintained after training.

If increases in the strength and recruitment of cortical networks/inputs excited by TMS occurred, training probably affected existing spared connections rather than recruiting, on a large scale, new areas of motor-related cortices. This is supported by the observation that the location where the largest MEP response could be evoked, or hot spot, did not change appreciably after training (see Table 1). In most cases, hot spot coordinates were centered over the leg area of the primary motor cortex (1 cm lateral and 1 cm posterior to vertex) (Petersen et al. 2001), suggesting that training increased the function of spared projections from the primary motor cortex and did not recruit, on a large scale, premotor and supplementary motor areas as seen for the affected hemisphere during stroke (Liepert et al. 1998; Trompetto et al. 2000). However, assessing the loci of plasticity with TMS, especially for the leg area, is very difficult and these other nodes of the sensorimotor network, in addition to cerebellar, reticulospinal and propriospinal networks, most likely contributed to enhancing corticospinal and motor function (Dobkin 2000).

Correlation between improvements in walking function and corticospinal tract function

The percent increase in connectivity of the corticospinal tract, or \( M_{\text{max}} \), was positively and significantly correlated to the amount of improvement in locomotor function as assessed by the increase in WISCI II score, the distance a subject could walk in a 6-min period, and the increased peak locomotor EMG activity. Although the preceding correlation does not prove unequivocally that increases in the strength of the corticospinal tract cause improvements in walking function, the data do provide strong evidence that increases in corticospinal tract function have relevance to the trained motor behavior (see also Fraser et al. 2002). Information as to the relationship between the time course of MEP increases and improvements in locomotor function would help to determine the role of the corticospinal tract in mediating locomotor recovery from training. For example, in one subject (7M) who was tested at 2 mo into a 4.5-mo training trial, both \( M_{\text{max}} \) and WISCI II scores reached maximal values at 2 mo even though walking distance and weight bearing continued to improve over the next 2.5 mo. These initial observations suggest that the corticospinal tract...
plays a larger role in improving walking skill rather than walking endurance and strength. Future studies will examine the time-course of the increases in MEP responses in relation to functional improvements.

If increases in the function of the spared corticospinal tract do mediate, in part, training-induced improvements in walking, then it is important for subjects to concentrate on voluntarily activating their leg muscles during treadmill training. By using slow walking speeds and allowing subjects to activate their muscles independently as much as possible, subjects in this study not only improved in their overground walking function but also in their ability to voluntarily activate their muscles in contrast to that shown in other studies (Wernig et al. 1999). Maximum voluntary intervention may occur when training is conducted at low speeds of walking (≈ 1.6 km/h) as was done in this study. However, training stroke patients at fast speeds of walking on the treadmill results in faster self-selected velocities of overground walking (Pohl et al. 2002; Sullivan et al. 2002). In addition, the more normal gait produced at higher velocities of walking may allow subjects to concentrate more on the overall gait pattern rather than on individual muscles (Pepin et al. 2003). Thus further studies examining the effect of training speed on locomotor reorganization in both acute and chronic injury are required.

In summary, our results demonstrate that improvements in corticospinal tract function and motor recovery can occur with intensive daily training, even many years after a SCI. These increases in corticospinal tract and motor function are long-lasting when tested in subjects that continue to use the new locomotor abilities gained from intensive training.

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