Effects of spinal cord injury-induced changes in muscle activation on foot drag in a computational rat ankle model

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Effects of spinal cord injury-induced changes in muscle activation on foot drag in a computational rat ankle model. J Neurophysiol 113: 2666–2675, 2015. First published February 11, 2015; doi:10.1152/jn.00507.2014.—Spinal cord injury (SCI) can lead to changes in muscle activation patterns and atrophy of affected muscles. Moderate levels of SCI are typically associated with foot drag during the swing phase of locomotion. Foot drop is often used to assess locomotor recovery, but the causes remain unclear. We hypothesized that foot drag results from inappropriate muscle coordination preventing flexion at the stance-to-swing transition. To test this hypothesis and to assess the relative contributions of neural and muscular changes on foot drag, we developed a two-dimensional, one degree of freedom ankle musculoskeletal model with gastrocnemius and tibialis anterior muscles. Anatomical data collected from sham-injured and incomplete SCI (iSCI) female Long-Evans rats as well as physiological data from the literature were used to implement an open-loop muscle dynamics model. Muscle insertion point motion was calculated with imposed ankle trajectories from kinematic analysis of treadmill walking in sham-injured and iSCI animals. Relative gastrocnemius deactivation and tibialis anterior activation onset times were varied within physiologically relevant ranges based on simplified locomotor electromyogram profiles. No-atrophy and moderate muscle atrophy as well as normal and injured muscle activation profiles were also simulated. Positive moments coinciding with the transition from stance to swing phase were defined as foot swing and negative moments as foot drag. Whereas decreases in activation delay caused by delayed gastrocnemius deactivation promote foot drag, all other changes associated with iSCI facilitate foot swing. Our results suggest that even small changes in the ability to precisely deactivate the gastrocnemius could result in foot drag after iSCI.

Foot drag could potentially be due to peripheral changes to muscle properties, changes in the timing of ankle muscle activations, changes to the shape of muscle activation profiles, related changes in joint kinematics, or all of these factors.

Changes in muscle properties can include atrophy and a shift toward faster-twitch, more fatigable fibers (Shields 2002). Muscle atrophy is not uniform after injury (Hutchinson et al. 2001). As antagonist muscles are differentially affected, there may be a shift in the force balance around the ankle joint. Foot drop could be associated with the efficacy of descending motor pathways (Wirth et al. 2008). While ankle muscle force is strongly influenced by spinal circuits (Hiebert and Pearson 1999), motor pathways are modulated by supraspinal drive, which is affected by injury (Chen and Wolpaw 2002). A reduction in supraspinal drive may reduce activation of some neurons while facilitating activation of others (Ettema 1997; Venugopal et al. 2011).

iSCI can cause changes not only in the relative timing of flexor and extensor activations but also in the overall shape of the activations (Domingo et al. 2007; Johnson et al. 2012; Thota 2004). Normal (sham injured or uninjured) rats show a roughly rectangular activation profile and an activation delay of ~40 ms between termination of the gastrocnemius (GAS) medialis (GM) muscle burst and the initiation of the tibialis anterior (TA) muscle burst. After iSCI, the activation profile of the GM begins with an initial high activation, followed by a gradual decrease and a smaller or nonexistent activation delay before the initiation of the TA burst (Thota 2004). Functional improvement can come from a return to a preinjury state or from compensatory changes in central control of locomotion resulting in a new gait pattern (Kaegi et al. 2001). Coordination among leg muscles can also be affected by iSCI (Johnson et al. 2012).

Kinematic changes in the ankle joint angle may potentially compensate for foot drag after iSCI. Changes in joint angles (with time) may alter muscle forces acting at the joint due to force-length and force-velocity properties. In rats, after iSCI the ankle has an increased range of motion (particularly over-extension) as well as loss of the second local maxima in the ankle trajectory during treadmill locomotion (Hillen et al. 2004). As rats experience many of the same secondary injury effects after iSCI as humans (Kwon et al. 2002; Onifer et al. 2007) and the course of rat hindlimb locomotor recovery after spinal contusion has been descriptively characterized (Basso et al. 1995), the rat provides a good model for evaluating foot drag following injury.
Severe injuries can further alter the gait pattern, leading to irregular gait (Cao et al. 2005). Hyperextension and hyperflexion of the ankle could also contribute to foot drag (Barbeau et al. 1999). Kinematic changes may be compensatory or harmful with regard to locomotor outcomes by selectively increasing or decreasing the force-generating capability of individual muscles at specific points in the gait cycle.

We tested the general hypothesis that iSCI-induced alterations in muscle coordination consist of negative (maladaptive) and positive (adaptive) changes that characterize the loss and recovery of foot swing after injury. First, we hypothesized that changes to coordination among antagonistic muscles about the ankle result in inappropriate coactivation and inability to flex the ankle at the stance-to-swing transition. However, adaptive changes could potentially mitigate some of the maladaptive effects of inappropriate coactivation. Specifically, we hypothesized that changes to locomotion kinematics, muscle atrophy associated with mild iSCI, and changes to the shape of the neural activation of the GAS may reduce the effects of inappropriate coactivation at the stance-to-swing transition and reduce foot drag. To test these hypotheses, we used empirical data obtained from normal and iSCI rats to construct a computational musculoskeletal model of the rat ankle and used this model to assess the causes of foot drag. Our results suggest that even small changes in the ability to precisely deactivate ankle joint muscles could lead to the foot drag commonly observed after iSCI.

Materials and Methods

Musculoskeletal and locomotor data were collected from 12 adult female Long-Evans rats (270–300 g), 6 sham injured and 6 with a mild-moderate T8 vertebral (T9 spinal) spinal cord contusion injury (iSCI). All rats were kept on a 12:12-h light-dark cycle with ad libitum food and water. The study was approved by the Institutional Animal Care and Use Committee (IACUC) of Arizona State University and complied with the Guide for the Care and Use of Laboratory Animals. The musculoskeletal and locomotor data were used to develop a musculoskeletal model and simulation framework to test the hypotheses with a hybrid of forward (muscle forces) and inverse (joint angles) dynamics models.

Spinal cord injury procedure. Rats were randomly selected to undergo either sham or mild-moderate contusion injury. Surgeries and contusions were performed as described in Hillen et al. (2013). Briefly, under anesthesia, a U-shaped laminectomy was performed at the T8 vertebrae for all animals. For animals in the contusion (iSCI) group only, a mild-moderate contusion (154 ± 3 kdyn) was performed with a force-controlled impactor (IH Instruments). After surgery, animals were allowed to move freely in their cages for 4 wk, during which the Basso, Beattie, and Bresnahan (BBB) 21-point locomotor score (Basso et al. 1995) was assessed for the animals every day for the first week and each week thereafter to verify injury severity (BBB scores reported in Fig. 2 of Hillen et al. 2013).

Musculoskeletal properties for model development. At the end of the fourth week after injury, rats were euthanized under heavy anesthesia and the hindlimb was separated from the remaining tissue. Superficial muscles were removed, and the hindlimb was mounted on a rigid frame. Clamps were attached to the foot and pelvis. Tie wrap was used to hold the tail and spinal column and suture was used for additional support along the body. Tension was maintained along the axis of the leg (thus the knee and ankle were fully extended) to maintain stability in the absence of a clamp on the femur or tibia. Muscle attachment points for ankle muscles and visible bony prominences were measured with a custom-designed aluminum probe consisting of a flat surface with six reflective markers and a coplanar sharp tip (Fig. 1A). The location of the tip was calculated from the locations of the six markers. Marker distances were verified with a calibrated digital caliper. For each measured point, the tip of the probe was held just touching the point of interest, and two infrared-sensitive video cameras with colocolated infrared light sources recorded 2 s (120 frames) of data. A 36-point calibration object was used to orient the cameras and calculate marker distances. Error in the system was <0.5% in position and <1.5° in angle (Thota et al. 2005). Video was collected directly into Vicon Peak-Motus and then digitized and preprocessed into three-dimensional (3D) marker locations before export to MATLAB for tip calculations. For each visible combination of three reflective markers, the location of the tip was calculated with vector algebra. 3D tip location was calculated by averaging all three-marker calculations over all 120 frames. No more than two markers were obscured in any particular measurement. All points were then transformed into local coordinate systems (Fig. 1B). The foot coordinate system was defined by the following sets of axes: X: malleolus midpoint (0,0,0) to 2nd and 5th metatarsal midpoint, Y: X crossed with medial to lateral malleolus, and Z: X crossed with Y. The lower leg coordinate system was defined by the following axes: X: condyle midpoint (0,0,0) to malleolus midpoint, Y: X crossed with lateral to medial condyle, and Z: X crossed with Y. 3D position data were captured for seven animals (3 sham injured, 4 iSCI).

After attachment point measurement, hindlimb muscles were carefully dissected and placed in lactated Ringer solution. Details of the muscle parameter data have been presented previously (Hillen et al. 2013). Dissected muscles used in this model included TA, GM, and gastrocnemius lateralis (GL). Mass, density, fiber length, sarcomere length, and pennation angle were collected (reported in Table 1 of...
Hillen et al. 2013). For two sham-injured animals, the external tendon for both the GAS and TA was measured ex vivo with a digital caliper. Differences in musculoskeletal geometry between sham-injured and iSCI groups were analyzed by nonparametric t-tests with P < 0.05. All statistical analyses were run in SAS (SAS Institute, Cary, NC).

Musculoskeletal computational model. A two-dimensional (2D) model of the rat ankle with one rotational degree of freedom was constructed in the SimMechanics add-on for MATLAB/Simulink R2009b (Fig. 2). Ankle joint geometry (ankle center of rotation and muscle origins and insertions) was averaged from data collected from seven animals (3 sham injured, 4 iSCI). The lower leg and the foot were each modeled as a single rigid segment connected by a single rotational degree of freedom for the ankle (Fig. 3A). No upper leg was included, and thus the effect of knee motion was excluded. Modeled muscle attachments for both muscles included one origin and one insertion point. The via point for the TA was used as its insertion for moment arm calculations, with the fixed length between the via point and true insertion added in for muscle length calculations. Via points

Fig. 2. Musculoskeletal model organization. A combined forward dynamics and inverse dynamics approach was utilized for development of the musculoskeletal model. Muscle model Simulink blocks were formulated from base Virtual Muscle cat data, supplemented with collected rat musculoskeletal parameters. Muscles were driven by simplified neural drive profiles and ankle joint kinematics, which were converted into muscle lengths with the experimental skeletal geometry. Muscle force output was converted into joint moment with dynamic muscle moment arms from the skeletal model. If net ankle moment was positive during a small window at the stance-to-swing transition of the selected kinematic profile, the trial was determined to have successful foot swing. If the net moment was negative, the trial was said to indicate foot drag. Dashed lines indicate the unused portion of a closed-loop system. By breaking the loop before calculating kinematics, we are able to make behavioral predictions in the absence of segment properties, ground reaction forces, and numerical instabilities inherent to traditional forward dynamics simulations.

Fig. 3. Musculoskeletal model components. Musculoskeletal model structure and time-varying inputs. A: model includes lower leg fixed to ground attached to a foot with a single-degree rotational joint. Gastrocnemius (GAS) and tibialis anterior (TA) muscles are attached between the 2 segments. B: muscle activation was varied between rectangular and trapezoidal profiles, and the activation delay was varied from positive (a gap) to negative (overlap/coactivation) values. C: ankle joint kinematic profiles used to determine muscle lengths for sham injury, iSCI, and dragging conditions. Note the overextension and lack of a second local minima in the iSCI trajectory. Dragging was a theoretical profile assuming that the foot had been dragging for at least 1 entire step cycle before the current foot swing attempt. D: muscle moment arms for the TA and GAS muscles for sham injury, iSCI, and dragging kinematics conditions.
for the GAS origin were omitted, as the knee and upper leg segment were lumped with the lower leg so the moment around the knee was excluded.

Hill-type models were used to calculate muscle force based on activation electromyogram (EMG) profiles, calculated muscle lengths, and calculated velocities from the mechanical model. Muscle models were constructed with Virtual Muscle 4.0.1 for MATLAB/Simulink R2009b (Cheng et al. 2000; Song et al. 2008). Virtual Muscle is an expanded Hill-type model with a contractile element that incorporates muscle force-activation, force-length, and force-velocity properties scaled by muscle physiological cross-sectional area (PCSA) and muscle specific tension (Brown et al. 1999; Brown and Loeb 2000).

\[ F_m(t) = f(v) \cdot f(l) \cdot a(t) \cdot F_m^{\text{max}} \]  

(1)

where \( F_m(t) \) is the force of the muscle at time \( t \), \( f(v) \) is the normalized velocity-dependent force, \( f(l) \) is the normalized length-dependent force, \( a(t) \) is the time-varying muscle activation level (0–1), and \( F_m^{\text{max}} \) is the maximum isometric muscle force. \( F_m^{\text{max}} \) is then determined by multiplying PCSA by specific tension (Sacks and Roy 1982). Virtual Muscle uses the following simplified PCSA equation assuming a muscle density of 1.06 g/cm:

\[ \text{PCSA} = \frac{\text{muscle mass}}{\text{muscle density} \times \text{fascicle length}} \]  

(2)

Default parameters for mammalian muscle from Virtual Muscle (Brown et al. 1999; Brown and Loeb 2000) were used except where noted below. Experimentally measured muscle mass, fiber length, fiber pennation angle, and free tendon length values were used. Measured fiber lengths were converted to optimal fiber lengths by multiplying with the ratio of relaxed sarcomere length to rat average sarcomere length [2.4 \( \mu \text{m} \), from the literature (Burkholder and Lieber 2001)]. Only one type of fast fiber was used because, while ignoring fatigue, both kinds of type II fibers have similar dynamics (Botterman et al. 1986; Kernell et al. 1983). Recruitment was approximated with the continuous recruitment model (Song et al. 2008). Parallel and series elastic components representing the passive properties of the muscle tissue were also included (Fig. 4). Elastic elements were modeled with a log/linear relationship (Brown et al. 1996). Muscle in-series aponeurosis in the GAS was modeled by adding to the external tendon measurement: \( 2 \times (\text{both ends}) \) the cosine of the pennation angle multiplied by measured fascicle length \( L_f \) (measured as fiber length above). The TA was modeled similarly, but only 1×, as the TA contains little to no origin aponeurosis (Magannaris and Paul 2000). Lateral and medial heads of the GAS were summed or averaged, where appropriate, from GM and GL. Ankle kinematics from treadmill walking were used to determine the movements of the modeled leg, from which instantaneous muscle lengths, velocities, and moment arms were calculated with model geometry.

**Simulation of factors contributing to foot drag.** Simulations were developed to determine the effect of each factor (muscle activation delay, muscle activation shape, joint kinematics, and muscle atrophy) on the incidence of foot drag. Muscle kinematics and muscle activation patterns were used as inputs to the muscle model to calculate muscle forces. Experimentally collected ankle angle trajectories (Fig. 3C) were imposed on the model from which muscle lengths and moment arms were calculated (Fig. 3D). With dynamic muscle length and dynamic muscle activation level, dynamic force was calculated with SIMULINK’s ode4 Runge-Kutta fixed step solver with a \( 1 \times 10^{-5} \) s time step. Moments about the ankle due to each muscle were calculated from muscle force and anatomically determined moment arms, from which net ankle moments were calculated as the sum of all muscle moments acting around the ankle joint. One stance phase was simulated. Maximum net ankle moment was assessed for a 40-ms window at the stance-to-swing transition. The assessment window was limited to this period to determine foot swing, as forces developed after the stance-to-swing transition would not prevent drag. If this value was positive, the trial was defined to have foot swing; if this value was negative, the trial was defined to have foot drag.

**Parameter variation.** Four parameters varied between trials: ankle kinematics, muscle activation latency, muscle activation shape, and muscle strength. Three sets of ankle treadmill kinematics (at 21 m/min) were used (Fig. 3C). Two kinematics conditions were used from previously reported data: an averaged trace from sham-injured rats (BBB: 21) and an averaged trace from iSCI rats (BBB: 15.6 ± 2.4 SD), showing a loss of the local maxima before stance and overextension during stance (Hillen et al. 2013). A third kinematic condition, foot drag kinematics, was estimated as ankle angle maintained at 155°, approximating an inconsistent dragging gait where the foot was dragging prior to the modeled step-to-swing transition (unpublished observation in experimental studies). While the animals in this study did not show foot drag at the time of data collection (4 wk after injury), they did drag their feet during the recovery process. This is common to animals recovering from mild-moderate contusion injuries, as reflected by their early BBB scores where stepping does not occur or the animal steps using the dorsal surface of the foot (Hillen et al. 2013). Neural drive was modeled by exaggerating differences in EMG burst durations determined from measurements of intact Long-Evans rats walking on a treadmill (Thota et al. 2005). The TA burst was set to begin 50 ms prior to initiation of foot swing and to be 88.5 ms in duration. TA activation magnitude decreased from 1 to 0.4 during the burst. The GAS burst duration was set at 253 ms, with its start and end times defined by the muscle activation latency parameter. The latency between the end of the GAS activation and the beginning of the TA activation was varied between ~10 ms (10-ms

![Fig. 4. Modified Hill-type muscle model. The muscle model is an expanded Hill-type model whose contractile element incorporates muscle force-length and force-velocity properties, scaled by muscle physiological cross-sectional area and muscle specific tension. A: physiological representation of the muscle. B: schematic representation of the muscle. Parallel and series elastic (PE and SE) components representing the passive properties of the muscle tissue as well as a contractile element (CE) are included. SE is constructed from aponeurosis and external (free) tendon. C: components that contribute to the contractile element model include length, velocity, and activation level.](http://jn.physiology.org/content/early/2016/10/20/jn.00507.2014.full-000507-2014fig4.png)
coactivation of the GAS and TA muscles) and 50 ms (a 50-ms gap between TA and GAS muscle activations) in increments of 10 ms to show responses from coactivation through normal activation profiles. GAS activation shape was varied by changing the activation profile between rectangular (GAS activation magnitude at 1 for the entire burst) and trapezoidal (GAS activation magnitude decreasing from 1 to 0.5 during the burst; Fig. 3B). These two shapes are simplified forms of the activation profiles reported for uninjured animals moving at the same speed (Thota 2004), which exaggerate the differences between the two groups. Muscle strength differences were simulated by varying muscle mass between normal (100% each) and moderate iSCI (100% TA, 80% GAS) (Hutchinson et al. 2001) in order to study the effect of muscle atrophy due to iSCI. Of the measured or input parameters (those changed from the base muscle model), changes in muscle moment arms had potentially the largest effect on the results (Ackland et al. 2012; Hunter et al. 2009). Muscle (TA and GAS) insertion points on the foot were varied independently ±5% in a single increment from the measured values to determine the sensitivity of the model to these parameters.

RESULTS

Musculoskeletal parameters. Musculoskeletal parameters obtained to develop the computational model showed no significant differences between sham-injured and iSCI groups in the musculoskeletal attachment points or joint centers (Table 1). Both the GAS and TA had no measurable origin tendon. The insertion tendon was 10.4 ± 0.2 mm for the GAS and 14.6 ± 2.1 mm for the TA as measured in two sham-injured and two iSCI animals. Averaged across all model conditions, a (±5% change in TA insertion point position had a (+0.027 N-cm/−0.007 N-cm) change in net ankle moment and a (±5% change in GAS insertion point position had a (−0.021 N-cm/+0.020 N-cm) change in net ankle moment (note the appropriate opposite signs for the different muscles).

Decreases in muscle activation delay can lead to foot drag. Deficits in muscle coordination can cause changes to activation delay and result in foot drag. Decreased activation delay causes decreased net ankle moment until foot drag is predicted (Fig. 5). As the GAS turns off later and later, there is an increase in overlap of moments produced by activation of the GAS and TA, decreasing the likelihood of a successful foot swing. The GAS is a stronger muscle (260% higher maximum force), with a 33% longer moment arm than the TA. Therefore, as the active periods of these two muscles become closer, extension moments caused by GAS activation exceed the flexion moments caused by activation of the TA and prevent foot swing. These findings support the hypothesis that changes to coordination among antagonistic muscles about the ankle could result in inappropriate coactivation and inability to flex the ankle at the stance-to-swing transition.

Changes to activation shape can reduce foot drag. iSCI kinematics and, to some degree, muscle atrophy can counteract the effect of decreased activation delay to allow foot swing. Trapezoidal activation increases net ankle moment by an average of 0.15 N-cm (Fig. 5B) compared with a rectangular activation profile. The gradual decrease in ankle moment provided by trapezoidal activation of the GAS reduces negative ankle moment at the end of stance and allows activation of the TA to overcome the remaining GAS force, even with some coactivation. These data support the hypothesis that changes to GAS activation shape could contribute to reducing foot drag.

Muscle atrophy facilitates foot swing. Muscle atrophy increased the region of foot swing (Fig. 5). All “no-atrophy” models (dashed lines in Fig. 5) produce lower net moments than moderate-atrophy models (solid lines in Fig. 5). For moderate atrophy, the likelihood of successful foot swing is increased. The muscle atrophy profile seen after moderate injury (80% GAS, normal TA) shifts the moment ratio toward the TA, allowing flexion caused by its activation to overcome the extension caused by activation of the GAS. This effect is not large, however (each solid line is ~5% above its paired dashed line).

Alteration in kinematic profiles after iSCI increases likelihood of foot swing. Ankle extension increased by 12%, resulting in a 0.34 N-cm increase in net ankle moment at the stance-to-swing transition when simulating kinematics associated with iSCI compared with kinematics associated with sham-injured animals (Fig. 5). This increase in force was likely due to muscle force-length properties. Changes in kinematics associated with iSCI shifted the GAS to the descending region of the force-length curve, allowing the TA to more easily generate enough force to allow foot swing. Moreover, adoption of kinematics associated with dragging in the previous step substantially changed the sensitivity of net ankle moment to all other factors; all four possible combinations with a drag profile are nearly linear in Fig. 5, with no variation between any factor combinations (Fig. 5, A and B). In this case, the GAS is too long to generate forces strong enough to overpower the TA with any combination of muscle atrophy, activation delay, or activation profile. These data support the hypothesis that changes to locomotion kinematics after iSCI could act to reduce the effects of inappropriate coactivation.

Stepping kinematics and activation delay have greatest influence on stance-to-swing transition. Although several factors affected ankle moments at the stance-to-swing transition (with positive values promoting foot swing and negative values promoting foot drag), not all factors had equivalent effects (Fig. 6). In Fig. 6, activation delay was collapsed to two physiological values, −0.01 s (iSCI) and 0.04 s (normal). Stepping kinematics and activation delay had the largest effects on net ankle moment. For kinematic profile, drag resulted in an average increase in net ankle moment of 0.56 N-cm (the largest effect) and iSCI of 0.34 N-cm over sham-injured kinematics. Activation delay (from 0.04 s to −0.01 s) increased net ankle moment by 0.33 N-cm. Activation profile and muscle atrophy increased net ankle moment by 0.15 and 0.07 N-cm, respectively. Variations of 5% in muscle insertion points had a

Table 1. Musculoskeletal geometry

<table>
<thead>
<tr>
<th>Point</th>
<th>Position, cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foot</td>
<td></td>
</tr>
<tr>
<td>Ankle</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>TA insertion</td>
<td>0.19 ± 0.16</td>
</tr>
<tr>
<td>GAS insertion</td>
<td>−0.33 ± 0.08</td>
</tr>
<tr>
<td>Lower leg</td>
<td></td>
</tr>
<tr>
<td>Ankle</td>
<td>−4.10 ± 0.10</td>
</tr>
<tr>
<td>TA origin</td>
<td>−0.50 ± 0.10</td>
</tr>
<tr>
<td>GAS insertion</td>
<td>0.00 ± 0.00</td>
</tr>
</tbody>
</table>

Values are means ± SD; data collected from 7 animals [3 sham injured, 4 incomplete spinal cord injury (iSCI)]. Ankle joint is defined as (0,0), positive values are more distal. Three-dimensional position values were projected onto the single line segments. No significant differences were seen between groups. TA, tibialis anterior; GAS, gastrocnemius.
smaller effect than any other experimentally varied parameters (−0.007 to 0.027 N-cm).

**DISCUSSION**

Use of a 2D model of the rat ankle to determine the possible causes of foot drag following iSCI led to three main findings: 1) muscle coordination affects locomotion performance (i.e., foot drag); 2) stepping kinematics and muscle atrophy profiles observed after injury may be adaptive, contributing to reducing foot drag during locomotion; and 3) the shape of muscle activation profiles may also substantially affect performance.

The results of this model reflect the force balance among flexor and extensor muscles in the ankle at the stance-to-swing transition. The simulations illustrate that changes to burst pattern and activation delay have opposing effects on coordination. A decrease in activation delay acts to decrease net ankle moment at the stance-to-swing transition by allowing the residual force in the GAS to overpower the smaller TA, impairing proper foot swing. However, a change to a trapezoidal activation shape for the GAS could reduce GAS activation as the stance-to-swing transition is approached, decreasing residual GAS force and increasing dorsiflexion moment. Therefore, a trapezoidal activation profile could reduce or prevent foot drag. The standard deviations of the effects are large, as they represent the variability of the results observed across the set of prescribed model conditions, not due to random variation (Fig. 6B). The large standard deviations in these parameters (particularly in activation delay and kinematics) indicate that they play a prominent role in determining foot drag for some model conditions. Finally, ±5% variations in muscle attachment points and the resulting effects on muscle moment arms did not alter these conclusions.

Net ankle joint moment was used as an outcome measure to assess foot drag for two reasons. First, at the stance-to-swing transition the ankle is free to move and positive net moment can overcome gravity and result in foot swing. Therefore, ankle moment can be more easily correlated to gait performance at the stance-to-swing transition than at other phases of gait. Second, joint moments could reflect muscle strength, which is often an indicator of recovery (Fukunaga et al. 2001). Force in the ankle extensors has been implicated in control of the stance-to-swing transition (Ekeberg and Pearson 2005). However, impairment in muscle strength does not necessarily correlate with recovery of gait after injury (Wirth et al. 2008). Our finding that inadequate muscle coordination could substantially affect ankle moment at the stance-to-swing transition could
potentially explain why recovery of muscle strength or activation alone does not allow full recovery of gait (Johnson et al. 2012).

The importance of muscle coordination to motor performance demonstrated by our model for rat iSCI is consistent with potential causes of deficits that have been identified in humans. After iSCI, human subjects lose the ability to complete voluntary single-joint movements and lose reciprocity between flexor-extensor pairs (Maegele et al. 2002). Coordination deficits may be due to alteration in circuits controlling coordination in the limbs, specifically those involved in flexor-extensor coordination (Kiehn 2006), possibly allowing overlap in activation of agonist-antagonist pairs (Kaegi et al. 2002).

Assumptions and limitations. Several assumptions and simplifications of our approach potentially affect our interpretations. Simplified neural drive patterns were used for the model muscle activation profiles. Although these patterns substantially simplify neural activation for each simulated trial, the variation in activation parameters that we used allowed us to exaggerate the effects of changes in activation patterns in a physiologically relevant range. Moreover, while the activation parameters used in this model-based study have been associated with SCI, we are not aware of experimental studies that have directly measured the effects of activation parameters on foot drag.

Our model did not include the passive properties of the rat ankle or passive elements within the muscles themselves (Wu et al. 2012). However, passive properties influence movements at intermediate angles and velocities less than at extremes, and therefore are unlikely to substantially affect the patterns that we observed. The moment arms calculated for our muscles are similar to those reported in a previous study (Johnson et al. 2008) for GAS but 17% lower for TA, possibly because of differences in via point implementation. Lower moment arms could potentially change the specific predicted time of the stance-to-swing transition but would not be expected to change the overall conclusions that activation delay, activation shape, kinematics, and atrophy all affect gait performance.

Our model was simplified, in that we simulated one step cycle and measured net moment only at the stance-to-swing transition. However, the same factors that influence the stance-to-swing transition could potentially influence other aspects of movement.

Our model used a hybrid inverse-forward dynamics simulation of locomotion. Forward dynamics simulations have been successfully used in many contexts but typically require information from many muscles, extensive assumptions about muscle activation, and simulation of ground contact and segment inertial properties (McGowan et al. 2010; Neptune et al. 2009). The technique of combining forward and inverse dynamics that...
we employed has been used previously to avoid computational difficulties involved in initial contact simulations (Meyer et al. 2007) and for efficiency of computation (Kistemaker et al. 2006). Open-closed hybrid models have also been used with success in control of (Mazurek et al. 2012) or improving optimization of (Higgison et al. 2012) musculoskeletal models. Consequently, the simplified model that we used represents a robust approach that allows for estimation of muscle forces and joint moments with a limited number of assumptions and complexity.

Stretch reflexes are known to change after iSCI (Thompson et al. 1992) and could possibly affect foot drag, as cocontraction is one strategy to attempt to compensate for decreased stretch reflex signals (Mazzaro et al. 2007). As we used whole muscle activation profiles, contributions of stretch reflexes would be included in net activation profiles, and therefore stretch reflexes need not be explicitly included in the model.

Foot drag can involve leg joints other than the ankle. Studies in cats have suggested that foot drag during treadmill walking may be due to impaired intralimb coupling between the hip and knee at the stance-to-swing transition (Rossignol et al. 2009). The effect of the knee joint on the mechanics of the ankle joint was not examined in this model. Knee kinematics could have effects on GAS muscle lengths and velocities, affecting the forces that develop in the muscle. Some studies suggest that GAS musculotendon length does not vary much across a wide range of knee angles in humans (De Monte et al. 2006) and that ankle muscle moment arms are similar across a range of knee angles in hopping mice (Ettema 1997). However, knee angle does have a significant effect on ankle range of motion in the human (Mitchell et al. 2008), so its effect could be analyzed in future work.

Muscle coordination could contribute substantially to foot drag after iSCI. Increased coactivation of agonist-antagonist pairs decreases net joint moments and can potentially decrease movement performance. Coactivation can also be seen as an adaptive behavior to increase joint stability. In unimpaired human subjects, or in the unimpaired side of a stroke subject, coactivation at the ankle is common and lends itself to stability (Lamontagne et al. 2000). However, in sensory (proprioception)-impaired individuals, stroke (Dyer et al. 2011), SCI (Leroux et al. 1999), and aging (Nelson-Wong et al. 2012), etc., cocontraction can lead to reduced motor performance. Our findings suggest that cocontraction after iSCI is maladaptive. However, muscle atrophy patterns seen in the ankle after injury (relative weakening of the stronger muscle) can potentially reduce the effects of cocontraction on foot drag. Atrophy may lead to decreased weight bearing and should be investigated further.

The timing of GAS muscle activation delay has a large effect on the net ankle moments at the stance-to-swing transition, supporting our hypothesis. Even small (8%) variations in the deactivation time for the GAS resulted in significant variations in net ankle moment causing foot drag in our simulations. In the absence of supraspinal input, forces at the ankle tend to synchronize muscle activity in the limb (Guertin et al. 1995). Changes to the ankle may, in turn, affect the balance between flexors and extensors of other joints.

Stepping kinematics after injury may be adaptive and contribute to reducing foot drag. When ankle kinematics took on a profile observed in injured rats (see Fig. 3C), the increased ankle angle near the stance-to-swing transition increased TA moments, allowing the TA to cause ankle flexion and overcome the GAS-driven extension and potentially reducing foot drag. Moreover, assuming that the foot had been dragging for the previous step cycle, foot swing was facilitated because of the weaker GAS force due to the effects of overextension on the muscle force-length properties. Therefore, observed changes to stepping kinematics may contribute to increasing net ankle flexion moments and reducing foot drag. A similar (to iSCI) kinematic pattern is seen in rats recovering with functional electrical stimulation (FES) therapy (Jung et al. 2009), which may further indicate that the alterations in locomotion (as demonstrated by kinematics) are an effective and functional adaptation, which would suggest that this deviation from the preinjury state should not be viewed as an impairment.

Shape of muscle activation profiles may substantially affect locomotor performance. Trapezoidal activation profiles do not produce as much force as rectangular profiles. Lower forces could be considered a limitation that could lower stance height or restrict weight bearing after injury. However, we have found that trapezoidal activation profiles could be adaptive by preventing excessive muscle coactivation during events such as the stance-to-swing transition. The specific time course of developing trapezoidal activation profiles after injury has not been determined. One possibility would be the initial development of an uncoordinated forelimb-hindlimb gait pattern (as seen in standard BBB score recovery progression; Basso et al. 1995), with the hindlimb adopting an alternating drag-swing pattern. Initially poor coordination among joints could be followed by a change in the shape of GAS activation as the rats develop coordinated gait. To determine the true time course, measurement of muscle activation (EMG) in injured animals over the entire time of recovery from iSCI is therefore an important next step.

Muscle atrophy facilitates foot swing. After iSCI, muscles in the distal limb can undergo changes similar to those seen in many disuse paradigms. Muscles atrophy, and muscle fibers shift toward faster-twitch, more fatigable fibers (Shields 2002). Muscle atrophy may not be applied uniformly to all muscles. The largest effects will be seen in muscles that undergo the largest changes in loading. For the ankle, the plantarflexors are likely to experience the largest changes to load, and the GAS undergoes more atrophy than the TA after iSCI in rats (Hutchinson et al. 2001). While this pattern can cause significant problems in load bearing, when addressing ankle-related foot drag it could actually be assistive.

Implications. The ankle plays a significant role in foot drag as well as other aspects of locomotion. During locomotion, ankle extensor muscle activation contributes to forward propulsion, body support, and forward leg acceleration during early swing (Allen and Neptune 2012). Ankle load modulates hip torque (Gordon et al. 2009, 2010) and contributes to the initiation of the stance-to-swing transition (Ekeberg and Pearson 2005; Hiebert et al. 1996; Wu and Schmit 2006). Ankle extensor afferents may excite, and thus help to coordinate, other extensors in the limb (Guertin et al. 1995). Hence, understanding the mechanisms for control of the ankle joint could also provide insight about hindlimb coordination (Rossignol and Frigon 2011).
Understanding the causes of foot drag may improve the effectiveness of devices designed to decrease foot drag after iSCI. FES of the common peroneal nerve (ankle dorsiflexion) has been used to increase walking speed and decrease foot drag (Thompson et al. 2011), and FES of the plantarflexor muscles has been used to increase gait speed after iSCI as well as assist in foot clearance of obstacles such as pavement curbs and stairs (Bajd et al. 1999). Mechanical ankle-foot orthoses have also been used for assistance in ambulation for those with drop foot (Chin et al. 2009). Understanding the properties of the native ankle may help in the development of control strategies used by such devices.

Conclusions. The results of our modeling study suggest that foot drag after iSCI could result from changes in muscle coordination that reduce appropriate activation delays between ankle antagonists. In animals with iSCI, failure to precisely deactivate the GAS muscle could result in foot drag. After iSCI, rats may use at least two strategies to reduce foot drag: alteration of stepping kinematics and adjustment of the shape of the GAS activation to a trapezoidal profile. Locomotor patterns in cats also adapt after complete SCI (de Leon et al. 1998; Mitchell et al. 2008). The use of a musculoskeletal model of the ankle joint suggests that some changes that are typically considered to be maladaptive may positively influence some aspects of locomotion such as foot drag. These findings suggest a hypothesis for the time course of recovery of foot swing. Initially after injury, flexor-extensor coordination is impaired, causing an irregular gait, with alternating foot swing and foot drag across the whole step cycle. As the animal recovers, the activation profile of its GAS muscle shifts to a trapezoidal profile, allowing foot swing despite continued intralimb coordination impairments. However, to determine the sequence of events and the cause of foot drag and following adaptation, a longitudinal study comparing cinematics (including any dragging) and muscle activations is needed.

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AUTHOR CONTRIBUTIONS

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