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Abstract

In this study, we investigated the responses to tread perturbations during human stepping on a treadmill. Our approach was to test the effects of perturbations to a single leg using a split-belt treadmill in healthy participants and in participants with varying severity of spinal cord injury (SCI). We recruited 11 people with incomplete SCI and 5 noninjured participants. As participants walked on an instrumented treadmill, the belt on one side was stopped or accelerated briefly during midstance to late stance. A majority of participants initiated an unnecessary swing when the treadmill was stopped in midstance, although the likelihood of initiating a step was decreased in participants with more severe SCI. Accelerating or decelerating one belt of the treadmill during stance altered the characteristics of swing. We observed delayed swing initiation when the belt was decelerated (i.e., the hip was in a more flexed position at time of swing) and advanced swing initiation with acceleration (i.e., hip extended at swing initiation). Furthermore, the timing and leg posture of heel strike appeared to remain constant, reflected by a sagittal plane hip angle at heel strike that remained the same regardless of the perturbation. In summary, our results supported the current understanding of the role of sensory feedback and central drive in the control of stepping in participants with incomplete SCI and noninjured participants. In particular, the observation of unnecessary swing during a stop perturbation highlights the interdependence of central and sensory drive in walking control.

NEW & NOTEWORTHY Using a novel approach with a split-belt treadmill, we tested the effects of hip angle perturbations to a single leg in healthy participants and participants with varying severity of spinal cord injury (SCI). A majority of participants initiated an unnecessary swing when the treadmill was stopped in midstance, although the likelihood of initiating a step decreased with the severity of SCI. Our results demonstrated interdependence of central and sensory drive in walking control.

INTRODUCTION

The effects of accelerations (slips) or decelerations (stops) of a treadmill on stepping patterns are likely to depend on the extent of supraspinal regulation of spinal locomotor centers (Jahn et al. 2008). In this study, we sought to obtain insight into the control mechanisms of gait by examining the stepping response to an acceleration or deceleration of the stance leg in people with varying severity of spinal cord injury (SCI). Since SCI interrupts supraspinal corrections to stepping perturbations (Dietz et al. 1995; Kuhn 1950), decreases descending drive to spinal locomotor systems (Hubli et al. 2011), and removes inhibitory regulation of spinal reflexes (Dietz et al. 2009; Hornby et al. 2003; Schmit et al. 2000), we expected that responses to treadmill perturbations would be altered with increasing injury severity. Specifically, we postulated that spinal reflexes would play a more prominent role in the responses to treadmill perturbations. The nature of these responses would provide insight into the role of sensory feedback and importance of supraspinal input on correcting perturbations to stepping patterns.

The cyclical, coordinated patterns of neural activity required for walking depend on both central drive as well as sensory signals from the limbs. Central pattern generators (CPGs), consisting of neural networks that produce cyclical, reciprocal coordinated movements of the limbs in the absence of sensory feedback have been observed in many vertebrate and invertebrate animals (see Kiehn 2006 and Minassian et al. 2017 for review). These CPGs are activated by descending drive and are believed to play an important role in the generation of neural activity for human walking; however, the locus of the neural substrate for the human locomotor CPG has been elusive (Ghosh and Pearse 2015; Hultborn and Nielsen 2007; Minassian et al. 2017). In addition, there is a plethora of evidence from animal models that sensory feedback is important for locomotion (Aiello et al. 2017; Berendes et al. 2016; Hunt et al. 2017; Rossignol et al. 2006). CPGs can also be activated and modulated with sensory feedback in the absence of descending control from the brain in animals (Cherniak et al. 2014) and in humans after a complete SCI (Hubli and Dietz 2013). Sensory feedback can contribute to rhythmic activity of the limbs,

playing a major role in the timing and magnitude of muscle activity (Acevedo and Díaz-Ríos 2013; Pearson and Ramirez 1997). In humans, the relative roles of central drive and sensory feedback in the generation of locomotor muscle activity are largely unknown despite their importance to the rehabilitation of walking, especially after SCI.

Treadmill studies in human infants also demonstrate evidence for sensory-driven control of locomotion, particularly from the hip afferents. The stance phase of infant stepping is shortened and swing phase advanced when the hip is extended, and there is termination of alternating flexor and extensor electromyography (EMG) patterns when the limb is held in midstance (Pang and Yang 2000). In adult humans with SCI, muscle activity occurs with leg movement when supported on a moving treadmill (Dietz et al. 1995; Wernig and Müller 1992). This activity is enhanced by sensory cues, as specific input related to loading (Harkema et al. 1997), muscle stimulation (Wu et al. 2011), walking speed (Beres-Jones and Harkema 2004), and augmented visual and proprioceptive feedback (Yen et al. 2014) can enhance motor output.

Aside from hip position, limb loading is another important sensory signal that impacts locomotion. Locomotion studies in animals and young infants have shown limb unloading is a cue for swing initiation (Conway et al. 1987; Duysens and Pearson 1980; Grillner 1985; Grillner and Rossignol 1978; Grillner and Zangger 1979; Hiebert and Pearson 1999; Pang and Yang 2000), and disruption of limb loading signals (lower lumbar regions) in trained spinal cats affects the transition between stance and swing phase (Norton and Mushahwar 2010). Consistent with these studies, people with SCI increase hip extensor activity in response to increased load at the ankle (Gordon et al. 2009, 2010). Although limb loading is a significant component of locomotion, this current study uses an experimental design that tests responses to changes in hip angle. Further discussion of sensory feedback on locomotor control will focus primarily on hip afferents.

In this study, we investigate the role of central drive and sensory feedback on locomotor control. We characterized the response to treadmill perturbations in 11 people with varying severity of SCI and 5 uninjured participants during treadmill stepping. We used a split belt treadmill to modify the gait cycle by means of unilateral treadmill belt perturbations and documented altered kinematics associated with the perturbations. We hypothesized that uninjured participants would rely strongly on central drive and that participants with SCI would have an altered sensitivity to sensory feedback in their response to the treadmill perturbations.

METHODS

Participants.

Participants with SCI were recruited through the Rehabilitation Institute of Chicago. Eleven participants with chronic (> 6 mo) motor-incomplete SCI took part in the study, with clinical characteristics described in Table 1. The mean age of the SCI participants was 47.9 yr (SD = 13.6 yr). Of the 11 SCI participants, 2 were female and 9 were male. Eight of the 11 participants were classified as American Spinal Injury Association Impairment Scale (AIS) D, and the remaining 3 participants were classified as AIS C. The Lower Extremity Motor Score (LEMS) and Sensory Score (T12 to S2 levels) of the American Spinal Injury Association (ASIA) exam were measured for each subject. All 11 participants with SCI had an incomplete lesion at the cervical or thoracic level of the spinal cord, presented intact flexor and stretch reflexes that were detected clinically, and had no previous history or evidence of peripheral nerve damage in the lower extremities, suggesting intact lumbar segments. Due to the treadmill walking requirement of the test, we only recruited participants who were able to take steps independently on a motorized treadmill. All participants with SCI had previous exposure to treadmill walking during therapy and demonstrated ability to independently take steps on a treadmill. We tested the limb that presented as the weaker side. Participants were medically stable, with no current medical illnesses, were not concurrently taking medications for spasticity or pain, and had medical clearance from their primary physician to

participate. Participants were excluded for unhealed decubiti, bladder or other infection, severe contracture or osteoporosis, heterotopic ossification, cardiac arrhythmia, or inability to give informed consent.

Table 1. Subject characteristics

ID	Age, yr	Gender	BMI	Month post injury	ASIA	Level	LEMS	T12-S2 Sensory	Community AT	Walking Status	Weaker side	Test leg	Gait Speed, m/s	BWS	Mean Handle Force, %body wt	Peak Handle Force, %body wt
P1	49	M	30.7	45	D	C6–C7	46	49	Wheelchair	Walker	R	R	0.4	0	0.77	2.72
P2	35	M	21.2	42.97	D	C6–C7	42	41	Wheelchair		L	L	0.6	0	3.01	11.62
P3	59	M	22.9	62.27	D	C5–C6	47	54	Walker	Walker	R	R	0.4	0	0.53	5.54
P4	28	M	28.3	9.93	D	C8–T1	50	38			R	R	0.6	0	2.03	6.22
P5	52	M	25.9	302	D	C5–C6	39	56	Wheelchair	Single cane	L	L	0.4	0	1.82	7.23
P6	62	M	30.4	443.73	C	T7	21	0	Wheelchair	Walker	R	R	0.2	30%	4.84	14.17
P7	65	F	21.1	103.93	D	T9–T10	44	62	Bilateral cane	Bilateral cane	L	L	0.4	0	5.00	12.29
P8	62	M	25.2	81.87	D	C4	41	15	Wheelchair	Single cane	R	R	0.4	0	0.85	6.02
P9	29	M	17.6	67.1	C	C3–C6	35	24	Wheelchair	Walker	L	L	0.2	0	0.92	4.91
P10	48	M	21.8	182.77	D	T5–T7	47	52	Bilateral cane	Bilateral cane	R	R	0.6	0	1.21	7.08
P11	38	F	43.7	77	C	T4	25	21	Wheelchair	walker	R	R	0.1	20%	1.50	12.92
C1	36	F	26.0				50	64				R	0.8	0	2.23	6.02
C2	27	F	21.5				50	64				R	0.65	0	0.03	0.28
C3	29	M	23.1				50	64				R	0.45	0	0.94	2.02
C4	35	F	24.4				50	64				R	0.5	0	1.59	4.18
C5	29	F	31.6				50	64				R	0.6	0	1.22	2.52

LEMS, Lower Extremity Motor Score of the American Spinal Injury Association (ASIA) exam; T12-S2 sensor, compiled sensory score from the ASIA exam; community AT, assistive technology used during community ambulation; walking status, minimal assistive device needed during walking; BWS, baseline body weight support; BMI, body mass index; M, male; F, female; R, right; L, left. *Participants P6* and *P11* needed BWS to endure walking for the duration of the experiment.

We also recruited five uninjured participants for the study. The mean age of the uninjured participants was 31.2 yr old (SD = 4.2 yr). Of the five uninjured participants, four were female and one was male. The uninjured participants had no known history of neurological disorders. Informed consent was obtained in writing from all participants before enrollment and participation in the study. All study procedures were conducted in accordance with the Declaration of Helsinki and with approval from the Northwestern University and Marquette University Institutional Review Boards. All tests were conducted in research laboratories at the Rehabilitation Institute of Chicago.

Experimental setup.

An eight-camera motion capture system (Motion Analysis, Santa Rosa, CA) was used to record three-dimensional movement of reflective markers placed on bony landmarks on both legs (Lewek et al. 2009). The 1-in. reflective markers were placed on the posterior sacrum, bilateral anterior-superior iliac spine, medial and lateral femoral condyles, medial and lateral malleoli, posterior heel of the shoe, and dorsally over the second and fifth metatarsal heads. Three markers were rigidly affixed on a thermoplastic cast that was secured on the thighs and the shanks.

The instrumented split-belt treadmill (Bertec, Columbus, OH) was equipped with independent six-axis force plates beneath each belt. The three-dimensional position of the markers, force plate data, and EMG data were collected using Cortex software (Motion Analysis). Customized LabVIEW software (National Instruments, Austin, TX) was written to control the speed of each treadmill belt according to the gait cycle of the participant. The gait cycle was determined in real time based on the center of pressure measured by the force plates (Roerdink et al. 2008). Heel strike was detected by monitoring changes in the medial-lateral axis of center of pressure in real time. Timing of the perturbation was calculated based on percentage of the period of a baseline gait cycle. All participants wore a harness during the entire duration of the study. The harness was connected to a two-dimensional trolley system above the treadmill that allowed the participant to move freely in the lateral and anterior-posterior direction. The participants had access to two instrumented handles, one the left side and one on the right side. Participants were given the choice whether to use the handles for stability (refer to Fig. 1).

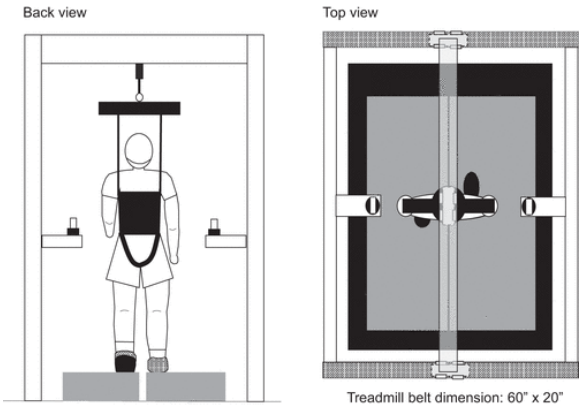

Fig. 1. Treadmill setup. Participants wear a harness while walking on the split belt treadmill. The harness is used to provide a safety mechanism to prevent falls and also to provide body weight support to the 2 participants that needed it for walking. Participants have access to 2 instrumented handles on the sides of the treadmill.

Perturbation.

Starting from 0 m/s, the treadmill speed was increased slowly according to the participant's response and adjusted until a comfortable speed was found. Participants were instructed to walk on the treadmill at their self-

selected comfortable walking speed (gait speed recorded in Table 1) and try their best to stay in the middle (anterior-posterior axis and medial-lateral axis) of the treadmill. Participants wore a pair of goggles in which the bottom half of the eye piece was covered with tape to prevent them from seeing the treadmill belts without completely blocking vision. Every five to eight steps (randomized), a perturbation was made to the treadmill belt on the test side. The perturbations were randomly chosen from stopping the treadmill belt (stop perturbation) for a duration of 0.5, 1, 1.5, or 2 gait cycles or speeding up the treadmill belt (slip perturbation) at 3 m/s^2 for 0.2 s. The stop perturbation duration was based on estimated gait period, calculated as the average of 10 calibrating steps. The perturbations were triggered at midstance of the gait cycle. The perturbation of speeding up the treadmill belt was inserted randomly with the stop perturbations to prevent the participants from getting accustomed to a stop perturbation and adapting their gait accordingly.

Stopping of the treadmill belt held the hip at the position of midstance, whereas speeding up the treadmill belt extended the hip and advanced the limb to the position for push-off. We reasoned that if gait control was dominated by sensory inputs, extending the hip would advance step initiation and holding the limb in hip flexion would delay and even stop the initiation of stepping. We anticipated that the slip perturbation would exaggerate the stretch reflex of the hip flexors, contributing to advancing swing initiation. The stop perturbation, on the other hand, would inhibit the hip flexor stretch by holding the hip in a flexed position. If step initiation occurred while the hip was in a flexed position during the stop perturbation, this would indicate a stronger central drive relative to sensory drive. However, if step initiation occurred after the stop perturbation only when the limb was being moved by the treadmill belt to reach the extended position, this would indicate a stronger sensory drive.

Data analysis.

Marker trajectories were used to track the limb kinematics using Cortex software (Motion Analysis). A subject-specific three-dimensional model of the pelvis and lower limb segments was built using Visual3D v4.85.0 (C-motion, Germantown, MD). The marker trajectories and ground reaction forces were low-pass filtered at 20 Hz and used to calculate the intersegmental joint angles and moments (e.g., hip angles and hip moments) using a rigid body analysis. Kinematics and kinetics data were exported for further analysis in MATLAB (MathWorks, Natick, MA).

While all step perturbations were analyzed, we initially considered the effects of the first stop perturbation. After the first stop perturbation, the participants might have adjusted the response to future perturbations, so the response to the first stop perturbation was considered separately. First, we determined whether the participants took a step during the first stop perturbation. We quantified the time between the previous heel strike and the first toe-off after the treadmill belt stopped, and data were normalized by the baseline step period. We checked whether the initiation of a step occurred while the belt was stopped or after the belt started moving again. Note that before the start of the experiment, the participants were told that the perturbation would consist of a change in speed of one of the treadmill belts, without an indication of the type of perturbation. This prevented the participants from anticipating and preparing a response to the first stop perturbation.

We identified the following gait timing events from each set of kinematic measurements: heel strike, toe-off, step period, swing, and stance phase duration. All timing characteristics were calculated for a baseline step before the perturbation and for the perturbed step, in both the test leg and the contralateral leg. We also measured the kinematic parameters of step height, stride length, and the hip angles at heel strike and toe off for each step. We monitored the ground reaction forces during the perturbation to ensure that the loading of the

limb was not changed drastically, as limb unloading is a cue for initiating swing (Conway et al. 1987; Duysens and Pearson 1980; Hiebert and Pearson 1999; Pang and Yang 2000).

Statistical analysis.

We hypothesized that the motor and sensory status of SCI participants plays a role in whether they initiated a step during a stop perturbation by examining step initiation from the time to first toe-off after the start of the first stop perturbation. Only the first stop perturbation was used in this particular analysis to minimize the effect of adaptation and subject anticipation. Based on the subjects' response to this first perturbation, we further classified participants into "stepper" and "nonstepper" categories (Table 2). We examined the difference in ASIA lower extremity motor and sensory scores between the participants who initiated a step and those who did not, using pairwise *t*-tests with a significance level at $P < 0.05$. To verify that the stop perturbations changed the hip angles, we further examined the difference in the hip angle at toe-off between baseline and the first stop perturbation using a two-way ANOVA repeated measures test with group (steppers and nonsteppers) and condition (baseline, first stop) as factors. Post hoc one-way ANOVA tests were used for comparisons between baseline and the first stop perturbation within each subject group to examine the change in toe-off hip angle due to the perturbation in each subject group.

Table 2. Demographics comparison between groups

	SCI			
	Nonsteppers	SCI Steppers	Control	*P* Value
Age, yr	49.4 (13.9)	45.3 (14.6)	31.2 (4.0)	0.061
BMI	28.1 (11.0)	25.2 (4.4)	25.3 (3.9)	0.7508
Months postinjury	132.0 (113.5)	127.2 (150.4)		0.9576
LEMS	35.0 (7.1)	42.4 (9.8)		0.2195
T12-S2 sensory	29 (18.4)	42.3 (20.3)		0.3096
Gait speed	0.28 (0.15)	0.46 (0.15)	0.6 (0.14)	0.019
Mean handle force,% body wt	1.27 (0.47)	2.49 (1.86)	1.19 (0.84)	0.2241
Peak handle force, %body wt	7.77 (3.56)	8.52 (4.19)	3.01 (2.185)	0.0491

Group means are computed for each of the subject groups, with the SD provided in parenthesis. SCI, spinal cord injury; BMI, body mass index;LEMS, Lower Extremity Motor Score.

For each trial, we then determined the values of the gait parameters (gait timing, step height, stride length, and hip angles) for the preperturbed steps (baseline) and the perturbed steps (stop perturbation and slip perturbation). We hypothesized that stop and slip perturbations change gait parameters in opposite directions. We calculated the mean of each parameter for all the steps in each condition (baseline, stop, and slip) for each subject. Significance in the difference in the timing, kinematic, and kinetic characteristics was determined using a two-way ANOVA repeated measures analysis, with participant group (uninjured participants, SCI steppers, and SCI nonsteppers) and perturbation condition (baseline, slip, and stop perturbation) as independent factors. The significance level was set at $P < 0.05$. For comparisons where the perturbation condition was significant, post hoc tests were performed with a one-way ANOVA between the various perturbation conditions within each subject group. The results of the post hoc ANOVA tests were used in denoting significance in the figures.

Using the data from the first stop perturbation, we determined whether participants made a step while the belt was stopped abruptly. Heel strike before the stop perturbation was used as a reference point. The time between this heel strike and the end of the stop perturbation was normalized by the baseline gait period and termed time

to end of perturbation (t_{end}). t_{end} Ranged from 1 to 3 baseline gait cycles, including the 0.5 gait cycle from heel strike to midstance in addition to the stop perturbation that ranged 0.5–2.5 gait cycle. The time between the reference heel strike and the first toe-off after the stop perturbation was normalized by the baseline gait period (t_{TO1}). If t_{TO1} was less than t_{end}, the participant made a step while the treadmill belt was stopped. Furthermore, if t_{TO1} was less than <1, the participant made a step within one baseline gait cycle. Figure 2*A* shows t_{TO1} plotted against t_{end} to display the results graphically.

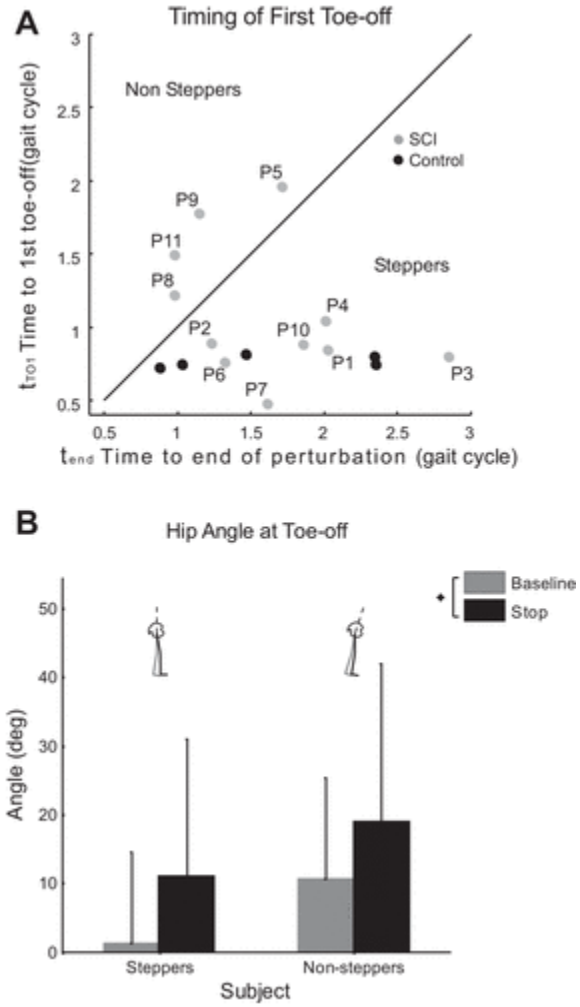

Fig. 2. Response to first stop perturbation. *A*: normalized first toe-off time (t_{TO1}), calculated as the time from the last heel strike to the first toe-off that occurred after the start of the stop perturbation, plotted against the time from the last heel strike to the end of the stop perturbation (t_{end}). The numbers beside the data points for the SCI participants indicate participant ID. Please refer to Table 1 for participant details, such as the Lower Extremity Motor Score (LEMS) and the T12-S2 sensory scores. The solid line indicates the unit slope line where a data point above the line indicates that the subject initiated a step during the stop period. *B*: hip angle at toe-off. The bar graph shows the hip angle at toe-off for the first stop perturbation. Error bars show the group SD. The stick figure above illustrates the kinematics for each condition. SCI, spinal cord injury; P, participant. *P= 0.05, statistically significant difference between the group or condition levels in the repeated measures ANOVA test.

The statistical analysis outlined above was performed in Statview (SAS, Cary, NC). The normality of the residuals on all the ANOVAs was tested using the Jarque-Bera test.

RESULTS

First response to stop perturbation.

In general, uninjured participants and SCI participants with less severe injury (higher motor scores) continued to step when the belt was stopped. All the uninjured participants and 7 out of 11 SCI participants took a step during the first stop perturbation. The participants who took a step during the stop perturbation took the step either within or very close to the duration of a baseline gait cycle. All participants with SCI who took a step during the stop perturbation had an ASIA LEMS of 42 or higher except for *participant P6*. The SCI participants who did not take a step during the stop perturbation (*P5*, *P8*, *P9*, and *P11*) scored relatively low on the LEMS (25–41). Detailed statistics of comparisons between the participant groups are reported in Table 2.

The nonsteppers had a lower mean speed compared with the steppers $P = 0.019$), although they had largely overlapping range of gait speeds (steppers: 0.2–0.8 m/s; nonsteppers: 0.1–0.4m/s). The average downward forces on the handles throughout the experiment was also analyzed for all the participants. The overall group difference between the three groups (steppers, nonsteppers, and controls) in the handle forces was not significant ($P = 0.22$); however, several of the SCI participants who took a step exerted almost three times the handle bar forces compared with the control participants.

Subjects initiated swing in a more flexed hip posture following the stop perturbation. Figure 2*B* shows the hip angle at toe off during/after the first stop perturbation, compared with baseline. The difference in hip angle at toe-off was significant compared with baseline ($P = 0.003$), but there was no significant difference between steppers and nonsteppers ($P = 0.313$). These results showed that the both uninjured and SCI participants initiated steps when their limbs were in a flexed position following the stop perturbation.

Aggregate responses to stop and slip perturbations.

We examined all trials (in addition to the first one) to quantify the characteristics of the steps immediately following the different perturbations (stop and slip). The steps that immediately followed the stop or slip perturbation were compared with baseline. In the following analysis, we also separated the SCI group into the seven steppers and the four nonsteppers, resulting in three subject groups (uninjured, SCI steppers, and SCI nonsteppers).

The variability in baseline step period was calculated to verify the consistency of the stop perturbation duration. The individual SD in baseline step period was small, ranging from 0.022 to 0.38 s. When expressed as a percentage of the mean step period of each individual, the variation was 1.5 to 8.4% of the step period for all individuals. This verified that the step period was relatively unchanging through time for both SCI subjects and control subjects, making the perturbation duration of 0.5 (50%) to 2.5 (250%) gait cycles valid and consistent throughout the experiment.

Gait kinematics.

The timing characteristics and other selected gait kinematics were altered by the stop and slip perturbations (two-way ANOVA; Table 3). The step period (time between successive heel strikes) was significantly different between subject groups and between perturbation types, with post hoc tests revealing longer step periods in SCI nonsteppers than uninjured subjects ($P = 0.012$). Figure 3*A* shows that step period was longer during a stop

perturbation and shorter during the slip perturbation and significant in both SCI groups (steppers: *P* = 0.010; nonsteppers: *P* = 0.016) but not for the uninjured group. Figure 3*B* shows a significant difference in the swing duration between groups, and Fig. 3*C*shows that the double stance duration was longer with the stop perturbation and shorter with the slip perturbation. Overall, the timing of the gait cycle changed with the perturbation, confirming that corrections for the perturbation were made within one gait cycle.

Table 3. Table of two-way ANOVA results for gait kinematics data

Measure	Between Subject Group *P* Value	Between Perturbation *P* Value
Step period	0.004*	<0.001*
Swing duration	0.107	<0.001*
Double stance duration	0.011*	0.006*
Step height	0.156	<0.001*
Stride length	0.815	<0.001*
Hip angle at toe off	0.356	<0.001*
Hip angle at heel strike	0.693	0.418

*Significant difference (*P* _ 0.05).

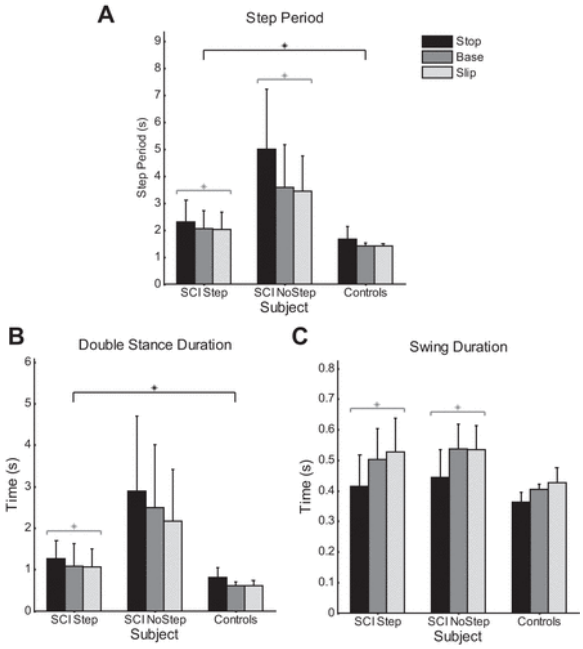

Fig. 3. Timing characteristics for responses to all perturbations. Bar graphs showing the differences between perturbations and subject group for step period (*A*), double stance duration (*B*), and swing duration (*C*). Error bars show the group SD. Double stance duration includes both double stance phase. SCI, spinal cord injury. Black asterisks indicate statistically significant difference between the group or condition levels in the repeated measures ANOVA test at *P* = 0.05. Gray asterisks indicate within group significance in the post hoc one-way ANOVA tests at *P* = 0.05.

The stop and slip perturbations also affected the step height and stride length. As shown in Fig. 4, the participants made longer and higher steps following a slip perturbation and shorter and lower steps following or during the stop perturbation, consistent with the timing corrections. Figure 5shows that while the hip angle at toe-off varied with the perturbation type, stride length strongly correlated with the hip angle at toe-off, maintaining a consistent hip angle at heel strike (Fig. 6). The R^2 values for the individual subject's linear regression between stride length and hip angle at toe-off ranged from 0.70 to 0.99 (means = 0.92; SD = 0.08; $P <$ 0.0001 for all regressions), showing very high correlations. The participants in all three groups maintained a consistent hip angle at heel strike regardless of the perturbation, suggesting hip posture at heel strike might be an important control parameter for treadmill stepping.

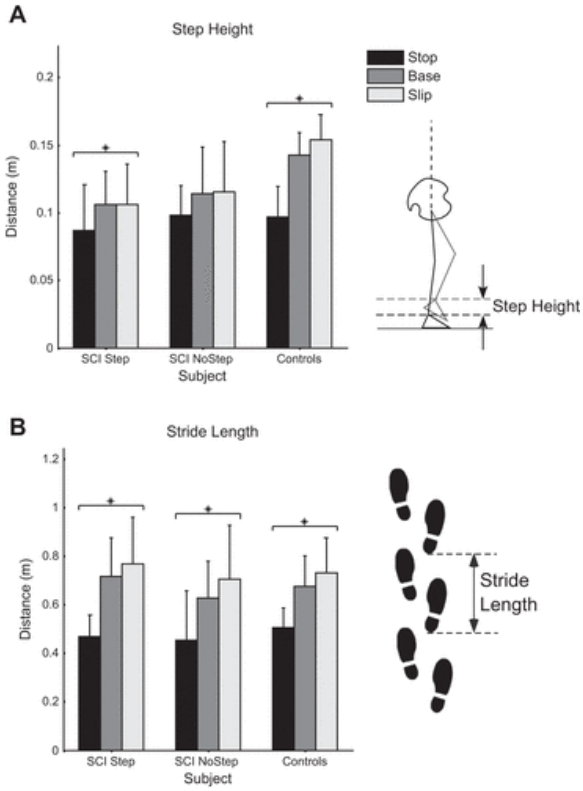

Fig. 4. Step characteristics for responses to all perturbations. Bar graphs showing the differences between perturbations and subject group for step height (*A*) and stride length (*B*). Error bars show SD. *Insets*: illustration of the definition for step height and stride length. SCI, spinal cord injury. **P* = 0.05, within group significance in the post hoc one-way ANOVA tests.

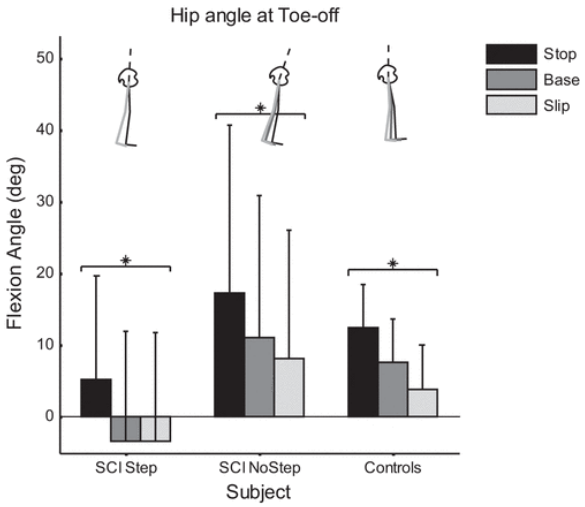

Fig. 5. Hip angle at toe-off. Bar graph showing the hip angle at toe-off for different perturbations and different subject groups. Error bars show the group SD. The stick figures illustrate the mean hip angle plotted in the bar graph. SCI, spinal cord injury. *P = 0.05, within group significance in the post hoc one-way ANOVA tests.

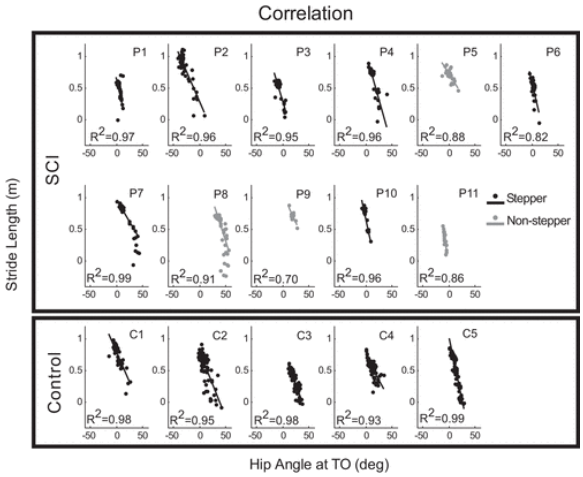

Fig. 6. Correlation between stride length and hip angle at toe-off (TO). Correlation between stride length and hip angle at toe-off for individual participants. Correlation coefficient (R^2) values are indicated on each plot. SCI, spinal cord injury; P, participant; C, control.

Ground reaction forces.

We monitored the ground reaction force to ensure that the loading was not affected by the perturbations, as loading is a factor for swing initiation (Grillner 1985; Grillner and Rossignol 1978; Grillner and Zangger 1979; Pang and Yang 2000). The vertical ground reaction force around the time of push off was not significantly different across subject groups (P = 0.1564) and perturbations (P = 0.420). This result indicates that the differences we observed between perturbations were a result of the changes in the hip angle.

DISCUSSION

In this study, we observed some gait characteristics that were independent of sensory input and others that correlated with sensory cues. In particular, hip afferent signals appear to be important for corrections to swing phase kinematics to maintain a consistent limb posture at heel strike, but it was apparent that central drive also played an important role in the control of gait, as steps were initiated in the stop perturbation case, when stepping could not have been triggered by sensory cues from the hip.

The influence of sensory systems on stepping depends strongly on afferent cues provided by the hip, which can be manipulated experimentally. When chronic spinal cats are placed on a treadmill with their weight supported, hip extension during late stance initiates swing, while holding the limb in flexion prevents swing initiation even though the contralateral limb independently continues the stepping pattern (Grillner and Rossignol 1978). In an immature corticospinal tract, human infants alter their stepping patterns similar to the chronic spinal cats when their hip angle is manipulated (Pang and Yang 2000). In adult humans with SCI, when supported on a moving treadmill, muscle activity occurs with leg movement (Dietz et al. 1995; Wernig and Müller 1992), and the motor activity is enhanced by sensory cues (Beres-Jones and Harkema 2004; Harkema et al. 1997; Wu et al. 2011; Yen et al. 2014) (Hubli and Dietz 2013). Sensory stimuli can also activate CPGs in animals in the absence of descending control from the brain (Cherniak et al. 2014).

The role of CPGs in human walking also remains unclear. Early evidence of locomotor CPGs was observed during fictive locomotion in cats, where the generation of rhythmic output occurs in the absence of movement or movement-related afferent feedback (Brown 1911; Chandler et al. 1984; Pearson and Rossignol 1991). In humans, there is no direct evidence of spinal CPG circuitry; however, rhythmic in-phase EMG bursts in the lower limbs and trunk have been reported in people with a motor complete SCI (Bussel et al. 1988; Calancie et al. 1994; Danner et al. 2015). Furthermore, a 1-s electrical stimulation applied to the thigh in humans with SCI triggers a flexor reflex that is followed by an extensor response (Wu et al. 2009), consistent with the half-center model of a locomotor CPG (Brown 1924). Prolonged, continuous electrical stimulation at the lumbar spinal cord in humans after SCI produces bursts of EMG activity in the lower extremities that results in movements of the legs, sometimes resembling gait (Dimitrijevic et al. 1998; Shapkova and Schomburg 2001) and additional evidence for central drive of locomotor pathways is provided by observations of gait following the loss of large myelinated sensory fibers below the neck in humans (Lajoie et al. 1996), suggesting that control of walking cannot rely solely on sensory feedback. Together, these observations of cyclical/reciprocal patterns of muscle activity indicate that CPGs likely play a role in human locomotion.

Recent evidence shows integration of supraspinal and afferent signals in patients with SCI. Submotor threshold stimulations (electrical and magnetic) that increase cortical excitability have been shown to prime the neural circuitry in patients with SCI and augment the input from sensory afferents in therapeutic interventions (Beekhuizen and Field-Fote 2008; Gomes-Osman and Field-Fote 2015; Hoffman and Field-Fote 2013) and reduce quadriceps spasticity (Estes et al. 2017). Individuals with complete SCIs have shown the ability to regain voluntary movement after intensive training with epidural stimulation (Angeli et al. 2014; Rejc et al. 2017) showing that even in complete SCI, there is potential for integration of supraspinal and afferent signals and a potential for the reorganization of spinal circuitry (Sayenko et al. 2014), adding to the complicated relationship between central drive and sensory feedback in locomotion after SCI.

Other control systems related to locomotion may be preserved in SCI and contribute to central drive of locomotion. Animal studies show that propriospinal, vestibulospinal, and reticulospinal connections may bypass the injury site and contribute to supraspinal control of stepping (Bareyre et al. 2004; Courtine et al. 2008; Drew

et al. 2002; Matsuyama and Drew 2000). Assessments of specific descending pathways show that each pathway has contributions to clinically measureable gait impairments in SCI (Barthélemy et al. 2015), but the mechanisms for recovery in humans are unclear.

Effect of spinal cord integrity on control of stepping.

The integrity of the spinal cord appears to be an important factor in how much sensory feedback was used in the control of stepping. Evidence from the current study suggests that swing initiation is triggered by hip sensory cues in people with more severe injury, whereas central drive appears to play a stronger role in step initiation in subjects with an intact spinal cord. The effect of the spinal injury itself is unclear. For example, a spinal injury might disrupt a distributed CPG network, reduce supraspinal excitation to spinal CPG networks, or alter the excitability of spinal locomotor reflex pathways. Regardless, the effect of injury severity on step initiation following a stop perturbation confirms the importance of supraspinal systems on motor control mechanisms for stepping.

The observations in four nonstepper participants with SCI were consistent with observations in analogous studies in infants. The stop perturbation in the current study was similar to the midstance disturbance in Pang and Yang (2000), where the limb was maintained in stance by holding a piece of cardboard beneath the foot. In infants, the disturbed limb stopped stepping while the contralateral limb continued to step, similar to the nonsteppers in the current study. The similarity of the more severe SCI subjects in the current study and infants is consistent with reports that myelination of the corticospinal tract is not complete until the age of 2 (Yakovlev and Lecours 1967), making the infant model similar to SCI in terms of supraspinal influence on spinal locomotor networks. Note that the relatively low incidence of nonsteppers in the current study is likely to be related to inclusion criteria "ability to step independently," which resulted in selection of mild SCI.

In noninjured participants and participants with less severe SCI, the persistence of bilateral stepping when one belt was stopped suggests an important role of central oscillators in the timing of stepping in the intact nervous system. These effects were pervasive, even overriding peripheral sensory cues indicating no need to initiate swing. While it is difficult to precisely assign contributions of sensory feedback and CPGs to walking in humans, a central oscillator is a viable explanation for the observation of continued stepping on a stopped belt.

The locus of central oscillators for gait and the relative participation of spinal and supraspinal systems in CPGs has been difficult to identify in humans. Even in animal models, it has been challenging to isolate components of CPGs for walking. The basic units of the CPG locomotor networks have been identified in lamprey, tadpoles, *Drosophila*, and crustacean models using genetic approaches (Grillner 2003; Kiehn and Kullander 2004; Suster and Bate 2002). Similar techniques applied to the mammalian spinal cord demonstrate multilevel CPG organization (Kiehn and Butt 2003; McCrea and Rybak 2008; Sharples and Whelan 2017). Evidence from locomotor training studies in people with SCI suggests that the human locomotor CPG might also be distributed throughout the spinal cord. After body-weight supported treadmill training, people with SCI produce foot motion that matches noninjured participants, yet recorded muscle activities in the lower limbs are drastically different (Grasso et al. 2004; Ivanenko et al. 2009). The spatial temporal map of motor neuron activity indicates reorganization of activities both above and below the spinal cord lesion, suggesting a distributed locomotor network (Grasso et al. 2004). Thus the SCI might disrupt the locomotor CPG network, leading to the nonstepping behavior observed for some subjects in the current study.

The halting of stepping after a stop perturbation in participants with more severe injuries suggests that sensory feedback from the hip is an important component of gait in SCI. People with SCI demonstrate heightened reflex

responses to movement stimuli, often resulting in complex, multijoint movements termed “spasms” (Benz et al. 2005; Little et al. 1989). In particular, the hip proprioceptors appear to play a critical role in triggering spasms (Schmit and Benz 2002) and in producing and modulating reflex activity throughout the legs during movement (Onushko et al. 2013; Onushko and Schmit 2007; Steldt and Schmit 2004). These observations are consistent with the responses in nonsteppers in the current study, in which the termination of hip movement associated with stopping the treadmill interrupted stepping in the associated leg. While hip proprioceptors are not the only source of sensory cues for stepping, we postulate that severe motor SCI increases the reliance on sensory feedback for the generation of stepping activity, akin to reflexive walking based largely on responses to hip movement.

Interestingly, *participant P6* had the lowest LEMS (21), and yet he took a step during the first stop perturbation. His strategy for walking differed from the other participants. Our analysis on the handle bar forces showed that he used the handle bars extensively to support himself (average of 5% body wt), in addition to the 30% body weight support that was provided through the harness. During single leg stance, the mean peak force he exerted on the handle bars was 14.2% body wt, highest among all participants. Due to the harness body weight support and the high amount of forces he exerted on the handle bars, he was bearing significantly less weight on his legs during walking compared with all other participants, which reduces the sensory stimuli to his legs. Furthermore, he was the only participant to score zero on the T12-S2 sensory examination and had been injured the longest (3 times longer than the average). With his lower extremity sensory processing severely impaired and extended duration since his injury, it is reasonable to speculate that he employed a more cognitive strategy to walking, based on timing rather than sensory input, where each step takes conscious effort. While using a cognitive strategy for walking is different from the automatic nature of walking with CPGs, a person employing a cognitive strategy to walking might take steps despite a stop in the treadmill belt if he or she did not perceive that the treadmill belt has stopped. If *participant P6* were excluded from the analysis, the difference between steppers and nonsteppers in sensory and motor scores becomes greater, and the results would suggest that those with both good sensation and motor strength scores are steppers. Despite these observations, we did not exclude *participant P6* from the statistical analysis as he completed the study and did not meet any of the study exclusion criteria.

Slip vs. stop perturbation.

The slip perturbation was introduced in the perturbation series as a catch trial to minimize the participant’s anticipation of the stop perturbation. In addition, slip and stop perturbations assess how sensory feedback and central oscillators impact stepping in SCI. Slip initiates a stretch reflex response and stopping the tread tests whether central oscillators continue to drive stepping in the absence of the stretch cue. In general, there is a tendency to associate reflexes, such as those triggered by tread acceleration (stretch of the hip flexors) with spinal systems, based on documentation of a corresponding spinal reflex in both animal preparations and injured humans (Adams and Hicks 2005; Bennett et al. 1996; Bessou et al. 1984; Dietz et al. 2009). In fact, supraspinal inputs might be expected to inhibit these spinal reflexes (Dietz 1987; Prochazka et al. 2002; Stein et al. 1993). In turn, pattern generators appear to have a spinal component but are influenced strongly by supraspinal drive, such as that associated with the mesencephalic locomotor region in animals (Jordan 1998; Ryczko and Dubuc 2013; Whelan 1996). Thus there is a tendency to associate sensory feedback with spinal systems (tread accelerations) and central oscillation with supraspinal drive (tread stops). In the current study, the perturbations and subsequent responses are not well designed to distinguish whether reflexes are spinal or supraspinal; however, the effects of injury severity appear to provide some support for previous observations.

The continued stepping with a stop perturbation decreased and response to hip stretch with a slip increased with more severe injury.

An important secondary observation of the current study was that foot position at heel strike was consistent, even when belt perturbations were altered. The slip perturbation extended the hip during midstance, as reflected in a more extended hip angle at toe-off, and the stop perturbation held the limb in hip flexion, as reflected in a more flexed hip angle at toe-off. When the hip was held in flexion, it resulted in longer double stance duration, shorter swing duration, and smaller steps. The stance duration, swing duration, step height, and stride length were all altered to compensate for the perturbation. These observations are consistent with corrections to locomotor patterns that are triggered by hip afferents in spinalized or decerebrate animals (Grillner and Rossignol 1978). Furthermore, the current results highlight the importance of sensory feedback, likely interfacing with a CPG (Van de Crommert et al. 1998) to maintain stepping patterns.

Sensory feedback is an important contributor to muscle activity during treadmill training of gait in people with incomplete SCI (Behrman et al. 2006; Roy et al. 2012). Our observations that stop and slip perturbations trigger corrective actions based on changes in hip angle is consistent with previous observations that the hip provides important sensory cues for swing initiation in people with SCI (Dietz et al. 2002; Dobkin et al. 1995). As a consequence, there is an increasing interest in applying sensory stimuli during treadmill training to augment appropriate muscle activity for gait. For example, constant electrical stimulation through spinal epidural electrodes, when combined with task-specific sensory cues, triggers appropriate muscle activity in a person with motor complete SCI (Harkema et al. 2011). Similarly, electrical stimulation applied to the skin over the hip flexors of the thigh enhances phasic muscle activity associated with treadmill stepping (Wu et al. 2011). The sensitivity of leg movement to stop and slip perturbations in nonsteppers (i.e., more severe SCI) in the current study supports the importance of sensory feedback in gait training.

Study limitations.

Although this study examined the contribution of supraspinal and peripheral sensory elements to the control of walking, there were limitations to the approach that affected interpretation of the results. Unfortunately, we did not have direct measures of the brain contribution to corrections for stop and slip perturbations and we can only to make inferences from the kinematic and kinetic measurements. Also, we did not completely eliminate visual feedback, and visual information from the surroundings may have influenced the reactions to the belt perturbations. We largely corrected for visual feedback by having participants wear goggles that block the lower half of their vision field, eliminating visual feedback of their legs and the treadmill. Furthermore, the alterations in treadmill belt speed changed the position of the whole limb and we could not limit the perturbation to stretch a single muscle group. Therefore, this study was limited in the ability to distinguish between different afferent signals in the limb.

There is concern that the difference in stepping responses in the participants with higher LEMS and those with lower LEMS might be caused by a difference in gait speed. That is, walking at a higher speed might result in higher inertia and larger forward momentum when the treadmill belt stopped, causing the person to take a step forward to maintain balance. While this is a potential contributing factor to the stepping response, all but one of nonsteppers had walking speed within the range of the steppers (SCI and non-SCI). Additional studies examining the response to stop perturbations at a wide variety of walking speeds in healthy controls will add to the understanding of the relationship between stepping response and walking speed.

The nature of the SCIs also affected the interpretation of the data. We had a large spectrum of injury among our SCI participants, in injury severity, injury level, and etiology of injury. Overall, the variation in the participant sample likely explained the large variability in the data, making it difficult to draw precise conclusions from some of the measures. The large variability in the SCI participants, the small number of subjects in the study and an unbalanced subject group also impacted the integrity of the statistical analysis and potentially increased the risk for type I errors in the statistics. Further studies with larger sample size are needed to confirm these findings. Due to the nature of the experiment, we were limited to recruit SCI participants who could take steps independently. Further studies are needed to examine the stepping response and stop and slip perturbations in participants with more severe impairments or motor complete SCI.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

V.W.T.C., T.G.H., and B.D.S. conceived and designed research; V.W.T.C. performed experiments; V.W.T.C. analyzed data; V.W.T.C. and B.D.S. interpreted results of experiments; V.W.T.C. prepared figures; V.W.T.C. drafted manuscript; V.W.T.C., T.G.H., and B.D.S. edited and revised manuscript; V.W.T.C., T.G.H., and B.D.S. approved final version of manuscript.

AUTHOR NOTES

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