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Kautz, S. A., C. Patten, and R. R. Neptune. Does unilateral pedaling activate a rhythmic locomotor pattern in the nonpedaling leg in post-stroke hemiparesis? Following stroke, locomotion is impaired and strongly associated with ineffective recruitment of paretic leg muscles. *J Neurophysiol* 95: 3154–3163, 2006. First published February 1, 2006; doi:10.1152/jn.00951.2005. Recent investigation in persons with clinically complete spinal cord injury has revealed that locomotor activity in one limb can activate rhythmic locomotor activity in the opposite limb. Although our previous research has demonstrated profound influences of the nonparetic limb on paretic limb motor activity poststroke, the potency of interlimb pathways for increasing recruitment of the paretic limb motor pattern is unknown. This experiment tested whether there is an increased propensity for rhythmic motor activity in one limb (pedaling limb) to induce rhythmic motor activity in the opposite limb (test limb) in persons poststroke. Forty-nine subjects with chronic poststroke hemiparesis and twenty controls pedaled against a constant mechanical load with their pedaling leg while we recorded EMG and pedal forces from the test leg. For the experimental conditions, subjects were instructed to either pedal with their test leg (bilateral pedaling) or rest their test leg while it was either stationary or moved anti-phased (unilateral pedaling). In persons poststroke, unilateral pedaling activated a complete pattern of rhythmic alternating muscle activity in the nonpedaling, test leg. This effect was most clearly demonstrated in the most severely impaired individuals. In most of the control subjects, unilateral pedaling activated some muscles in the nonpedaling leg weakly, if at all. We propose that, ipsilateral excitatory pathways associated with contralateral pedaling in control subjects are increasingly up-regulated in both legs in persons with hemiparesis as a function of increased hemiparetic severity. This enhancement of interlimb pathways may be of functional importance since contralateral pedaling induced a complete motor pattern of similar amplitude to the bilateral pattern in both the paretic and nonparetic leg of the subjects with severe hemiparesis.

INTRODUCTION

Locomotion poststroke is primarily impaired by ineffective recruitment of the muscles of the more affected leg (henceforth referred to as the paretic leg). Electromyographic (EMG) timing and magnitude are impaired during both walking (Knutsson and Richards 1979) and pedaling (Kautz and Brown 1998), which leads to reduced mechanical work output in each task (Kautz and Brown 1998; Olney et al. 1991). We recently found that bilateral pedaling in hemiparetic subjects exacerbated abnormal EMG timing of the paretic leg when compared with a mechanically equivalent unilateral pedaling condition (Kautz and Patten 2005). One possible explanation is that sensorimotor activity from the nonparetic leg facilitated abnormal paretic leg muscle activity.

Multiple studies have now documented that sensorimotor activity in one leg affects the motor output of the opposite leg. Studies in healthy subjects have revealed that sensorimotor activity in one leg strongly affects muscle output in biarticular muscles such as the rectus femoris and hamstrings (Kautz et al. 2002). Investigation in persons with clinically complete spinal cord injury (SCI) provides evidence to suggest that sensorimotor activity from the nonparetic leg may interfere with paretic leg pattern generation. Recent work conducted in persons with SCI has revealed that contralateral leg locomotor activity can activate rhythmic locomotor activity in the ipsilateral leg (Dietz et al. 2002). Dietz et al. induced stepping in patients with complete SCI and in neurologically healthy control subjects by using a powered gait orthosis (Lokomat, Hocoma AG, Zurich, Switzerland) in conjunction with a treadmill. Unilateral stepping was associated with bilateral leg muscle EMG activity in the healthy subjects. However, normal patterned EMG was demonstrated in only the stepping leg of persons with SCI. That EMG was only observed in the stepping leg of persons with SCI was interpreted as evidence that interlimb coordination depends on supraspinal input. However, Ferris et al. (2004) observed that rhythmic muscle activation was produced in the stationary and unloaded ipsilateral limb during both contralateral lower limb loading and movement in subjects with clinically complete SCI. Similarly, Kawashima et al. (2005) found that reciprocal contralateral leg motion amplified induced ipsilateral locomotor-like activity during a locomotor-like movement in subjects with complete SCI. Thus contrary to results from Dietz et al. (2002), the results from both Ferris et al. (2004) and Kawashima et al. (2005) suggest that interlimb coordination may not require supraspinal input. Nonetheless, although the role of supraspinal input remains unclear, these studies underscore the potential importance of contralateral sensorimotor input for activating an ipsilateral locomotor pattern.

Similar to the studies in SCI, our previous work in nondisabled individuals conducted using a pedaling paradigm has also demonstrated the importance of contralateral sensorimotor input. We have shown that the bifunctional thigh muscles

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(hamstrings and rectus femoris) responsible for limb transitions between flexion and extension are much more strongly influenced by contralateral sensorimotor input than other muscles (Kautz et al., 2002). Bifunctional muscles are more influenced than either the primarily unifunctional muscles responsible for flexion and extension of the limbs (hip and knee extensors and flexors) that produce most of the mechanical power during pedaling or the ankle muscles (tibialis anterior, gastrocnemius, and soleus) responsible for ankle dorsiflexion and plantarflexion that coordinate the transfer of power between the limb and crank. Thus even though the potency of interlimb influences is not known in persons with poststroke hemiparesis, evidence suggests they have the potential to contribute to the impaired paretic leg motor pattern.

The purpose of this research was to evaluate the influences on test limb motor output that arise from contralateral limb activity with the goal of identifying mechanisms that may have the potential to influence rehabilitation interventions that target locomotion and other bilateral lower extremity movements. We hypothesized that compared with similarly aged nondisabled individuals, there is an increased likelihood that ipsilateral rhythmic motor activity in the nonparetic leg would induce rhythmic locomotor-like motor activity in the contralateral paretic leg in persons with poststroke hemiparesis. Using a pedaling paradigm (e.g., 1-legged pedaling against mechanical loads typically experienced during bilateral pedaling), we tested the ability of unilateral pedaling to induce rhythmic activity in the individual muscles of the contralateral (test) leg when it was either stationary or moved passively. Induced contralateral leg activity was compared among paretic, nonparetic, and healthy legs. We further questioned whether induction of contralateral limb activity differs with hemiparetic severity as assessed using the Brunnstrom stages (e.g., dependence on abnormal synergies) (Brunnstrom 1970).

METHODS

Subjects

Forty-nine subjects with poststroke hemiparesis [36 males/13 females, 65 ± 9 (SD) yr] of >6-mo duration (56 ± 61 mo poststroke) and 20 similarly aged nondisabled subjects (11 male/9 female, 65 ± 6 yr) were recruited from the surrounding community. Hemiparetic subjects were selected if they had sustained a single, unilateral stroke and experienced at least mild residual lower limb paresis (Paretic side: 24R/25L) in the absence of severe perceptual, cognitive or sensory deficits, significant lower limb contractures or orthopedic impairment, significant cardiovascular impairments contraindicative to mild exertion (pedaling), and ability to tolerate sitting on a bicycle seat for ~1 h. All subjects provided informed consent as approved by the Stanford University administrative panels on human subject protections. The control subjects were screened for signs of neurological disease, lower limb orthopedic impairment, or cardiorespiratory disorders. The lower extremity and balance subsections of the Fugl-Meyer motor assessment (Fugl-Meyer et al. 1975) were performed on the hemiparetic subjects to provide an indicator of severity of motor impairment.

In an effort to determine the influence of hemiparetic severity on the propensity of unilateral pedaling to induce contralateral rhythmic activity, three separate groups of hemiparetic subjects were recruited on the basis of Brunnstrom motor recovery stages (Brunnstrom 1970). These subjects demonstrated a range of abilities to perform movements within and outside of extensor and flexor synergy patterns (e.g., Brunnstrom 1970). Subjects in the severe hemiparesis group (Brunnstrom stage 3, $n = 17$) were limited to movement within the synergy patterns (e.g., only basic limb flexion or extension synergies can be performed voluntarily). Subjects in the moderate hemiparesis group (Brunnstrom stages 4–5, $n = 16$) were able to produce some movement combinations outside of the synergy patterns, whereas subjects in the mild hemiparesis group (Brunnstrom stage 6, $n = 16$) were able to produce both isolated joint movements and movements in synergy patterns. Because the Brunnstrom stages and the Fugl-Meyer assessment are based on the concept of progression from one level of motor recovery to the next, we expected systematic between-group differences would be demonstrated in the Fugl-Meyer scores (mild = 96 ± 3, moderate = 87 ± 4, severe = 70 ± 12). The walking ability of the hemiparetic subjects in this study ranged from nonambulatory to mildly impaired.

Experimental apparatus

Our experimental apparatus allowed subjects to perform unilateral pedaling while a servomotor emulated a mechanical load similar to that normally encountered by the leg during bilateral pedaling. Fundamental to our design is a two-servomotor, split-axle pedaling apparatus (see Van der Loos et al. 2002 for detailed technical description of the apparatus) that allows mechanical decoupling of interlimb force generation such that the load experienced by the pedaling leg remains independent of whether the opposite leg pedals or remains resting (see Kautz and Patten 2005 for more detailed discussion). Briefly, during conventional pedaling, the load encountered by a pedaling leg is the load from the ergometer plus the load transmitted through the shared crank axle from the contralateral pedaling leg. To produce mechanically decoupled (MD) pedaling, the servomotor was programmed to emulate the total ergometer load experienced in two-legged pedaling, including emulation of the crank torque generated by the opposite leg in two-legged pedaling and emulation of the frictional/inertial load of the ergometer. Thus from a mechanical perspective, the MD-pedaling leg experiences the same mechanical load as during conventional bilateral pedaling. The servocontrol in the current experiment differs from that in Kautz and Patten (2005) in that the mechanical loads emulated were individualized to the paretic, nonparetic, or control leg of each individual subject. This approach represents an advancement over our previous use of a generic load experienced by the pedaling leg (paretic, nonparetic, or control). Pilot work suggested that the personalized loads did not alter the general characteristics of the pedaling pattern from those seen with the generic load. Instead, the main benefit was straightforward and precise matching of the workload for each subject.

The cranks of the split-axle pedaling apparatus were uncoupled, and each was driven by an independent servomotor (Kollmorgen B606A motor, D20 motor controller, 1-kHz servo loop; Kollmorgen Motion Technologies Group, Commack, NY). Data acquisition and servomotor control were implemented with LabVIEW 5.0 software. Custom real-time C software, accessible from LabVIEW, provided dual-motor servocontrol and data-acquisition for 32 analog channels and 4 encoder channels sampled at 1 kHz.

Our first step was to determine the mechanical load to be emulated for each leg during MD pedaling. This was accomplished by observing the subject pedal under a servomotor control mode (i.e., coupled-crank pedaling) that produced loads on the two pedaling legs that replicated the dynamics encountered with a conventional coupled-crank ergometer (i.e., flywheel inertia, belt friction and freewheeling). At 45 rpm, the emulated frictional load dissipated ~60 J. Control subjects performed one trial of coupled crank pedaling, and an algorithm (detailed in the following text) was used to determine the mechanical load experienced by the right leg. Once this subject-specific mechanical load was established, it was subsequently emulated for all three experimental conditions. Similarly, hemiparetic subjects performed two trials of coupled-crank pedaling, and an algorithm was used to determine the mechanical load experienced by the paretic leg from one trial and by the nonparetic leg from the other. The individualized limb-specific mechanical load determined for each leg was then subsequently emulated for MD pedaling with the same leg (i.e., paretic or nonparetic) during each of the three experimental conditions of the test (opposite) leg.

Algorithm for mechanical load determination

The mechanical load determination algorithm was based on recording the servomotor control torques during the coupled crank-pedaling mode. Coupled crank-pedaling was achieved by programming the servomotors so that there was a "master" crank and a "slave" crank. The slaved crank was position servocontrolled 180° out of phase with the master crank (i.e., its servomotor applied the necessary torque to always position the crank 180° out of phase with the other crank). The master crank was torque servocontrolled based on the sum of the emulated frictional and inertial workload and the torque applied to the slaved crank (as assessed by the slaved servomotor). Because the emulated frictional and inertial workload were defined a priori and the same for all subjects, they could be subtracted (in a post hoc analysis) from the recorded values of the total control torque applied by the master servomotor. The remainder of the control torque represents the individualized contralateral contribution to the ipsilateral limb's mechanical load, which was stored as a crank-angle-dependent function. In subsequent trials of unilateral pedaling, the control torques included this function, which reflected the sum of contralateral torque production and the torques representing the emulated frictional and inertial workload. Thus the emulated mechanical load was individualized for each subject because it contained the subject-specific contralateral leg contribution.

Experimental protocol

The experimental design allowed us to compare the rhythmic alternating muscle activity induced in the paretic, nonparetic and control legs (the test leg) when the opposite leg performed MD pedaling (the pedaling leg). The data presented in this study represent a subset of data collected in a larger study of bilateral coordination of hemiparetic locomotion. Each experimental session included additional conditions that will not be reported in this study.

We tested the left leg of the control subjects and the paretic and nonparetic legs of the hemiparetic subjects. For each test leg, the contralateral leg performed MD pedaling while the test leg performed one of three conditions that were presented in random order: pedaling (P), resting and stationary (S), and resting and passively moved (M). Thus control subjects performed three trials (1 leg × 3 conditions), whereas hemiparetic subjects performed six trials in two blocks of three trials (2 legs × 3 conditions). For the hemiparetic subjects, the order of conditions and the two legs tested were randomized within each block of three trials.

The three individual conditions were performed as follows. Subjects wore cleated ankle braces (DePuy Orthotech, Tracy CA) on each leg that could either be locked to fix the ankle at a specific angle or left unlocked to allow unrestricted ankle motion. For all three conditions of the test leg, the opposite leg performed MD pedaling with the brace left unlocked (i.e., analogous to a cleated cycling shoe). In the P condition (visually similar to bilateral pedaling on a conventional ergometer), the test leg's crank was offset 180°, antiphased from the MD-pedaling leg crank, by using position-servocontrol. The test leg's ankle brace was left unlocked, and the subject was instructed to pedal normally using both legs. In the S condition, the test leg's crank was held stationary by its servomotor at the forward horizontal position (90° relative to top dead center) with the ankle brace set to 10° plantarflexion. The subject was instructed to relax the test leg. In the M condition, the test leg's crank was offset 180° antiphased from the MD-pedaling leg crank using position servocontrol. The ankle brace of the test leg was locked at 10° plantarflexion to negate any need for muscle activity to control ankle kinematics. Similar to the S condition, the subject was instructed to relax the test leg as it was moved 180° antiphased to the MD-pedaling leg.

For each condition, an audible metronome tone was provided for ~10 s until a steady pedaling cadence was established at 45 rpm. The metronome was then turned off, and data collection was initiated. Subjects were instructed to pedal until asked to stop. Data collection commenced ~2–3 s after the metronome stopped and continued for 20–30 s. This approach was used to ensure that ≥10 consecutive revolutions of data were available for processing in each trial.

Data collection

Excess pelvic motion was minimized by using a shoulder and lap harness that attached to a backboard (parallel to seat tube of ergometer) to stabilize the subject and minimize movement relative to the seat. To minimize balance demands during all trials on the ergometer, subjects were supported on the bicycle seat and reclined against the backboard. The ankle braces were fitted with cleats that coupled with clipless bicycle pedals providing rigid attachment between the feet and pedals. The bicycle pedals were instrumented to allow measurement of both fore-aft and vertical pedal reaction forces (Van der Loos et al. 2002). Crank and pedal angles were measured using digital optical encoders.

Muscle activation patterns were measured bilaterally using surface EMGs from seven muscles: rectus femoris, biceps femoris long head, semimembranosus, vastus medialis, soleus, medial gastrocnemius, and tibialis anterior. All signals were sampled at 1,000 Hz. Analog RC anti-aliasing filters with low-pass cutoff frequencies of 80 and 800 Hz were used on non-EMG and EMG channels, respectively, to reduce high-frequency noise from the servomotor power amplifiers (~20 kHz). Note that the measurement methodology is consistent with recent studies from our laboratory and have been described previously (e.g., Kautz and Patten 2005).

Data processing

Test leg data were processed to determine the region in the crank cycle during which each muscle was maximally activated (if at all) in each of the conditions and a value for the EMG data when the muscle is considered to be minimally active. For each individual trial, pedal force and EMG data were collected as a function of crank angle over all consecutive complete crank revolutions that occurred in the 20-s trial (typically 8–12 revolutions). EMG data were rectified and smoothed (40-ms central moving average window). For each revolution, we determined Muscle_{win}, the location of the 90° window that contained the maximum amount of activity for each muscle (i.e., TA_{win} for tibialis anterior), and Muscle_{act}, the average magnitude within that window (i.e., TA_{act} for tibialis anterior; Fig. 1). For each revolution of the P condition, we also determined Muscle_{off}, the average magnitude in the 45° window that contained the minimum amount of activity for each muscle (Fig. 1). We considered Muscle_{off} to represent a baseline for the EMG activity that represents when the muscle is minimally active for each subject. Our previous experience with hemiparetic pedaling has shown that establishing a baseline during a resting trial (e.g., activity exceeding the mean resting value +3 SD) often leads to the conclusion that a muscle is active 100% of the cycle even when there are obvious bursts of rhythmic activity. Thus we established the Muscle_{off} criterion, as described in the preceding text, to be a conservative estimate of the EMG magnitude when a muscle is not receiving phasic excitatory input. For each muscle-trial-subject combination, the EMG data were normalized by the average value of Muscle_{act} for that subject during the P condition. As a result, average Muscle_{act} was always defined as 1.0 for the P condition. For the S and M conditions, Muscle_{act} expresses the ratio of the activity in that condition relative to the P condition (e.g., Muscle_{act} of 0.5 during the S condition would indicate that induced

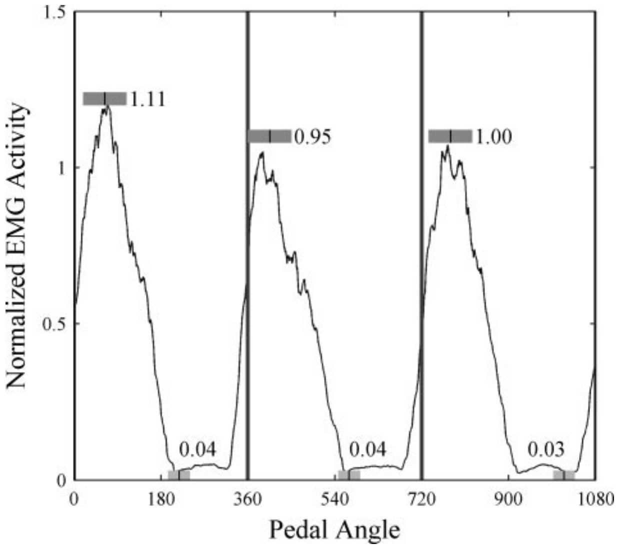

FIG. 1. Identification of $Muscle_{win}$, $Muscle_{act}$, and $Muscle_{off}$. Data shows smoothed electromyogram (EMG) during pedaling for 3 cycles of vastus medialis activity in the paretic leg of a subject with severe hemiparesis. The upper bars indicate the location of the 90° window of peak activity, $Muscle_{win}$, and the adjacent numbers represent, $Muscle_{act}$, the average magnitude of the activity in the window for that cycle. The lower bars indicate the location of the 45° window with minimum activity, and the adjacent numbers represent, $Muscle_{off}$, the average value in the window for that cycle. EMG data were normalized for each subject to the average value of $Muscle_{win}$ for the pedaling condition.

activity represents fifty percent of the activity observed in that muscle during the P condition).

The average tangential crank force (i.e., the component of the pedal force oriented perpendicular to the crank arm that acts to rotate the crank) was calculated as a function of crank angle for each revolution. The mechanical work output during the P and M conditions (work = average tangential crank force * crank length * angular distance through which the crank moves) was also calculated. The mechanical work associated with the S condition was not calculated because the motors were controlled such that the crank was kept stationary and there is no mechanical work associated with pushing on a stationary crank.

Data analysis

Descriptive statistics were obtained on the measures related to the seven muscles and mechanical work. To determine whether MD pedaling activates rhythmic alternating muscle activity in the opposite (paretic or nonparetic) leg for the three different groups of hemiparetic subjects (different levels of hemiparetic severity: mild, moderate, and severe) or in the opposite leg of a group of nondisabled control subjects, we compared $Muscle_{act}$ for the M and S conditions to $Muscle_{off}$ for the P condition. Each muscle was analyzed using the MIXED procedure of SAS software for comparisons of trial conditions stratified by leg and hemiparetic severity. For each trial condition, we included the individual calculations for each revolution (instead of using only a single mean value). Thus the model took into consideration the dependence of repeated measurements for each subject by including a random subject effect. We chose a significance level of $P < 0.001$ for within subject comparisons to make the test somewhat more conservative than testing whether activity exceeds the baseline value +3 SD. Because this conservative value represents >99.9% likelihood that means are actually different, we did not adjust the significance level for the total number of comparisons. Similarly, mixed models were fit to compare the three impairment groups (mild, moderate, and severe) stratified by leg and trial conditions. We chose a significance level of $P < 0.01$ for between subject comparisons and did not correct for the number of comparisons.

RESULTS

Muscle activity during pedaling

Consistent with the previous pedaling literature (e.g., Neptune et al. 1997, 2000), rhythmic alternating muscle activity was observed in control subjects in all muscles. Illustrated in Figs. 2 and 3, respectively, are an example of raw data and the timing of maximum activity $Muscle_{win}$ (the midpoint of 90° window with maximal average EMG). Primary muscle activations (reported in the following text as $Muscle_{win}$) observed in the test leg during the P condition were consistent with the three biomechanical function pairs previously described as

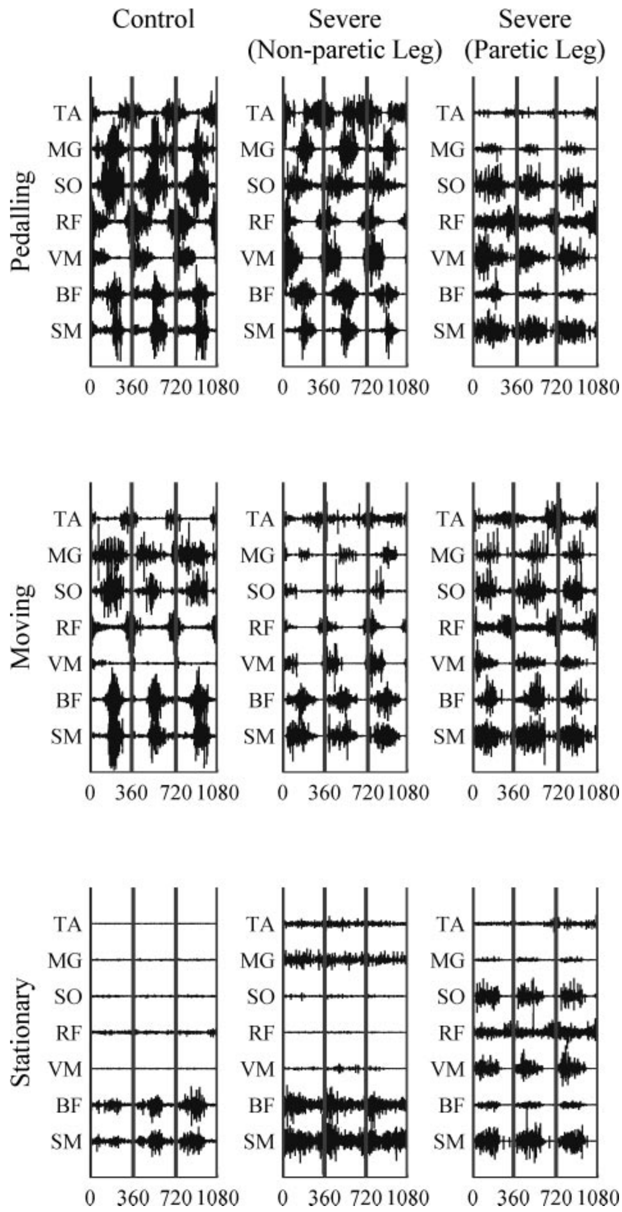

FIG. 2. Raw data for 1 control subject and the paretic and nonparetic leg of 1 subject with severe hemiparesis (3 consecutive revolutions are shown on 1 single trace) for all muscles and conditions. For each leg, the EMG data for each muscle are plotted at the same scale in each of the 3 conditions.

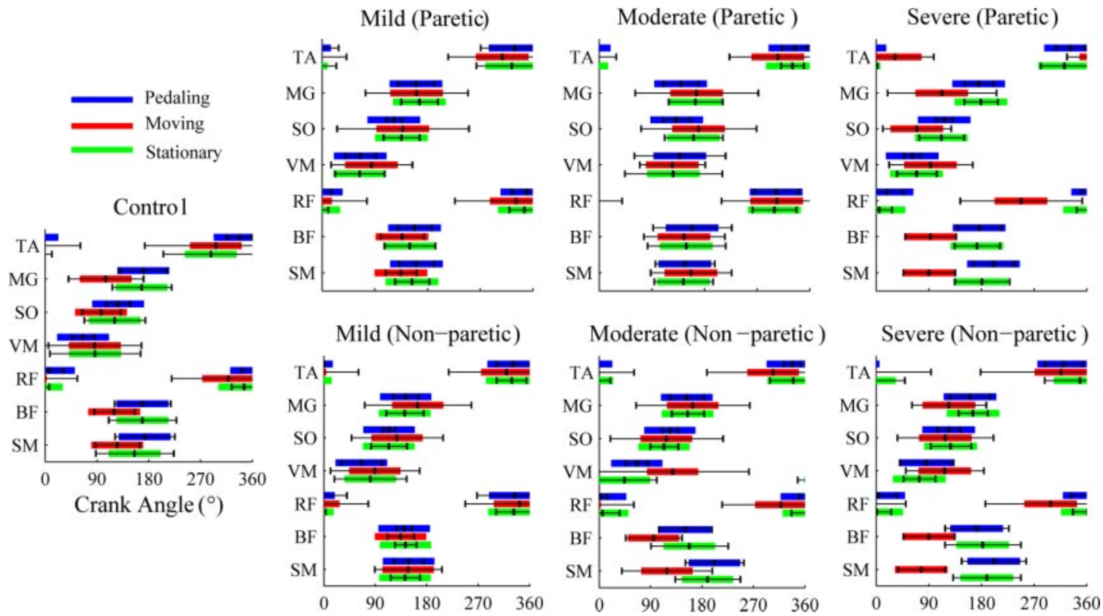

FIG. 3. Group average data for the timing of the 90° window of maximum activity, $Muscle_{win}$, for the control subjects and the paretic and nonparetic legs of the 3 groups of hemiparetic subjects (mild, moderate, and severe hemiparesis). Small bars represent mean ±1 SD.

necessary for successful pedaling (Neptune et al. 2000; Raasch and Zajac 1999; Ting et al. 1999). Rectus femoris (RF), biceps femoris long head (BF), and semimembranosus (SM) are bifunctional muscles whose activation (356, 169, and 173°, respectively) contributed to the biomechanical functions of limb transition (RF for flexion-to-extension and BF and SM for extension-to flexion transitions). Vastus medialis (VM) and soleus (SO) were activated in the leg extension phase (66 and 126°, respectively) and contributed to the extensor biomechanical function. Tibialis anterior (TA) and medial gastrocnemius (MG) were activated at 335 and 171°, respectively, such that they contribute to the dorsiflexor and plantarflexor biomechanical functions, respectively. $Muscle_{win}$ for each muscle is shown graphically in Fig. 3. The activation of paretic and nonparetic leg muscles in hemiparetic subjects also showed rhythmic alternating muscle activity consistent with that observed in previous pedaling studies (Kautz and Brown 1998). In general, $Muscle_{win}$ during the S and M conditions were grossly similar to the P condition.

Induced rhythmic activity in control subjects

During the S condition, rhythmic alternating muscle activity was induced in most muscles of the nondisabled control subjects [i.e., subjects performed MD pedaling with 1 leg while instructed to relax the other (test) leg, which was kept stationary]. Specifically, all muscles except TA and VM ($P > 0.001$) revealed induced rhythmic activation ($Muscle_{act}$ for S condition > $Muscle_{off}$, in the P condition $P < 0.001$). Raw data are illustrated in Fig. 2 and group averages for $Muscle_{act}$ are presented in Fig. 4. As revealed by SM activity greater than the activation during the P condition ($P < 0.001$), induced rhythmic activation was greatest in the hamstrings. However, BF activity did not differ from the P condition ($P > 0.001$). Low levels of induced rhythmic activation were observed in RF, MG, and SO during the S condition (i.e., between 0.17 and 0.27), but significant induced rhythmic activation was not observed in either TA or VM ($P > 0.001$). Because VM is the muscle that most directly represents power generation during pedaling, the group average of the VM EMG activity is presented graphically in Fig. 5.

During the M condition [i.e., subjects pedaled with 1 leg while instructed to relax the contralateral (test) leg, which was moved 180° antiphased to the pedaling leg], induced rhythmic activation was demonstrated in control subjects showed in all muscles (Figs. 2 and 4). SM again revealed induced rhythmic activation greater than during the P condition ($P < 0.001$). BF, TA, MG, and RF were activated less but still at substantial levels (i.e., between 0.51 and 0.65) as compared with the P condition. Activations of VM and SO were considerably lower (i.e., between 0.21 and 0.34). The mechanical consequences of the muscle activation during the M condition were small, as the 15 J of net work generated at the crank during the M condition was much less ($P < 0.001$) than the 48 J generated during the P condition (Fig. 6).

Induced rhythmic activity in nonparetic leg

In the nonparetic leg during the S condition, hemiparetic subjects showed induced rhythmic activation in all muscles except TA and MG in the mild subjects and VM in the moderate subjects (Figs. 2 and 4). With increased hemiparetic severity, no change in induced activation was observed. However, a nonsignificant trend for the induced activation to increase was observed in most muscles ($P > 0.01$). Overall, the patterns were mostly similar to those in the control subjects with BF and SM showing the greatest magnitude of induced activation: RF, TA, MG, and SO were activated at lesser magnitudes (greatest values for each muscle were between 0.20 and 0.46), and induced activation of VM was the lowest magnitude observed (0.17).

In the nonparetic leg during the M condition, hemiparetic subjects showed a substantial magnitude of induced rhythmic activation (always >0.36) for all muscles in all groups (Figs. 2 and 4). Again the overall patterns were mostly similar to those

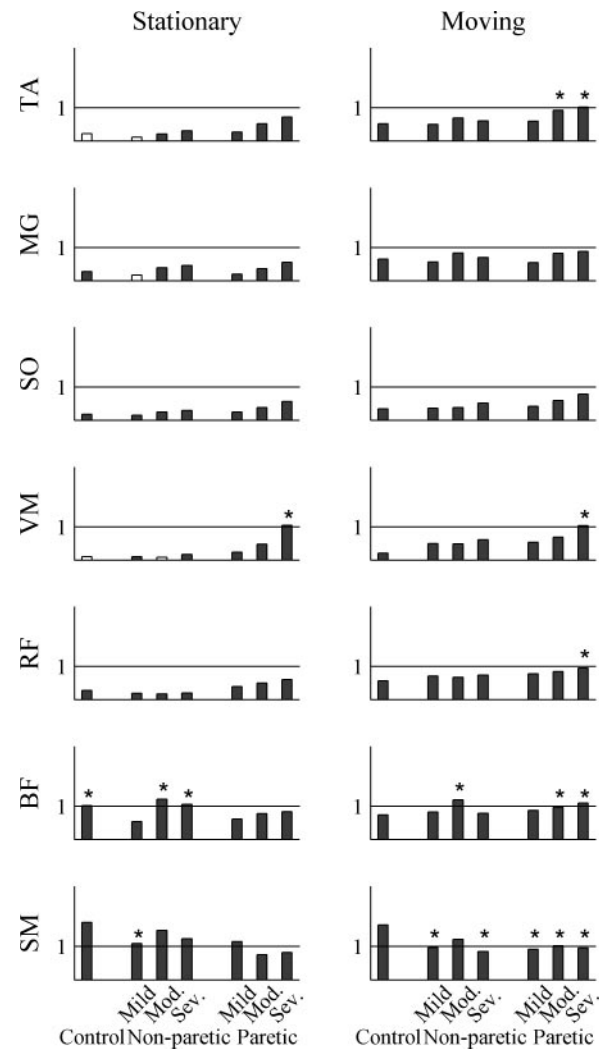

FIG. 4. Bars indicate the average magnitude of $Muscle_{act}$ for the stationary and moving conditions relative the pedaling condition (represented by the horizontal line at 1.0 because data were normalized to $Muscle_{act}$ during pedaling). The filled-in bars indicate that the muscle was activated in the pedaling condition. * indicates that the activity was not significantly different from the pedaling condition ($P > 0.001$).

observed in the control subjects with BF and SM showing the greatest magnitude of induced activation and RF, TA, MG, and SO activated at lesser, but still substantial, magnitudes (greatest values for each muscle were between 0.53 and 0.81). The major difference between the control and hemiparetic subjects is that induced activation of VM was of a substantial magnitude (0.48–0.61). Thus a complete pattern of rhythmic alternating muscle activity could be induced in the nonparetic leg during the M condition. The mechanical consequences of this facilitated muscle activation was substantial as the mechanical work done by the nonparetic leg in the mild, moderate, and severe groups was 37, 39, and 55 J during the M condition versus 58, 65, and 68 J during the P condition, respectively (Fig. 6). Note however that in all cases, the mechanical consequences were significantly less than during the P condition ($P < 0.001$).

Induced rhythmic activity in paretic leg

In the paretic leg during the S condition, the greatest magnitude of induced rhythmic activation was shown by the subjects with severe hemiparesis (Figs. 2 and 4). Overall, for the subjects with mild hemiparesis, the magnitudes of induced activation were mostly similar to those in the nonparetic leg, with BF and SM showing the greatest magnitude of induced activation, and RF, TA, MG, SO, and VM activated at lesser magnitudes (between 0.20 and 0.39). As hemiparetic severity increased to moderate, no change in induced activation was observed, although nearly all muscles revealed a nonsignificant trend for ($P > 0.01$) for induced activation to increase. As hemiparetic severity increased from moderate to severe, induced activation increased significantly in only VM ($P < 0.01$), although again a nonsignificant trend ($P > 0.01$) for the induced activation to increase was observed in nearly all muscles. However, comparisons between mild and severe hemiparetic groups revealed a significant increase in induced activation in TA, MG, SO, and VM ($P < 0.01$). The induced activation of VM in the paretic leg of the severely hemiparetic subjects (1.05) did not differ significantly from the magnitude of activation during pedaling. (The similarity of these activation patterns is illustrated in Fig. 7). Thus the paretic leg of the mildly hemiparetic subjects behaved similarly to the control legs of nondisabled during the S condition (with the exception of increased activation of VM). In the same condition, severely hemiparetic subjects showed significantly more activation than the control and mildly hemiparetic legs.

In the paretic leg, during the M-condition hemiparetic subjects demonstrated substantial induced rhythmic activation (always >0.50) for all muscles at all levels of hemiparetic severity (Figs. 2 and 4). Overall, as observed in the control subjects, BF and SM showed the greatest magnitude of induced activation, whereas RF, TA, MG, SO, and VM were activated at lesser, but still substantial, magnitudes (between 0.43 and 1.04). As temiparetic severity increased from mild to moderate, only TA and MG revealed greater induced activation ($P < 0.01$), although there was a nonsignificant trend ($P > 0.01$) in nearly all muscles for induced activation to increase. As hemiparetic severity increased from moderate to severe, induced activation increased only in VM ($P < 0.01$), although again a nonsignificant trend ($P > 0.01$) for induced activation to increase was observed in nearly all muscles. As was observed in the non-paretic leg, comparisons between mild and severe hemiparetic groups revealed a significant increase in induced activation in TA, MG, SO, and VM ($P < 0.01$). The paretic leg of the severely hemiparetic subjects revealed a markedly increased magnitude of induced activation as TA, RF, VM, BF, and SM did not differ significantly ($P > 0.001$) from the magnitude of activation observed during pedaling. The magnitudes of MG and SO, were 0.88 and 0.78 (Fig. 4). The mechanical consequences of muscle activation were substantial as the mechanical work done by the paretic leg in the mild, moderate, and severe subjects was 30, 19, and 1 J during the M condition versus 42, 26, and 3 J during the P condition, respectively (Fig. 6). Note that the work production during the M conditions in both the moderate and severe subjects were not significantly different from those during the P conditions ($P > 0.001$).

DISCUSSION

Unilateral pedaling by persons with poststroke hemiparesis can activate a complete pattern of rhythmic alternating

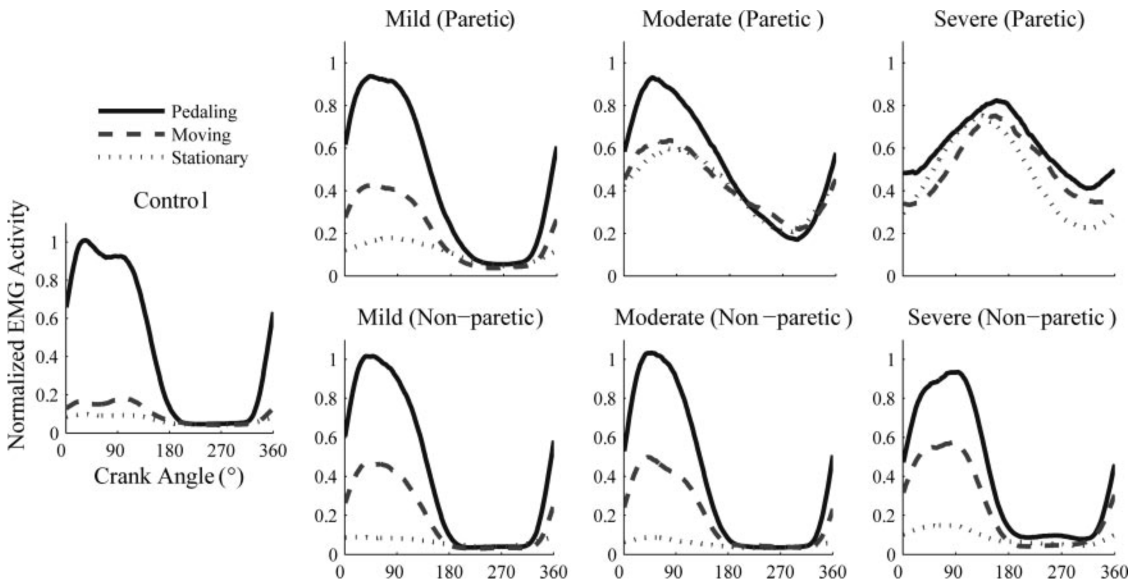

FIG. 5. Group averages for vastus medialis EMG in the different conditions. Prior to averaging, EMG were smoothed with a 40-ms moving average and normalized to the average activity in the "on" window during the pedaling condition. Of particular note is the very low level of activity during the stationary condition in the control and nonparetic legs.

muscle activity of substantial magnitude (i.e., all muscles are activated) in the nonpedaling leg. This induced activation is observed in either a stationary or moving paretic leg or in a passively moved nonparetic leg. In contrast, unilateral pedaling is able to activate some functions only weakly in the contralateral leg of most nondisabled control subjects. For the subjects with severe hemiparesis (Brunnstrom stage 3, those dependent on limb synergies), induced rhythmic alternating muscle activity in the paretic leg during passive movement reaches nearly the same magnitude as that observed during pedaling and greater than half of the magnitude of the pedaling pattern when the limb is held stationary.

Unilateral pedaling induces individual muscle activation differently depending on both the primary biomechanical function to which the muscle contributes and the severity of poststroke hemiparesis. For muscles contributing to limb transitions, unilateral pedaling induced substantial activation in all subjects, including both hemiparetic and nondisabled controls, in both the stationary and moving conditions. Muscles contributing to plantar/dorsiflexion biomechanical functions were activated when moving but were either weakly activated (MG and SO) or not activated (TA) when stationary in control subjects. It is important to recall that the ankle was braced during the moving and relaxed conditions, so little change in ankle joint position occurred during these conditions. Accord-

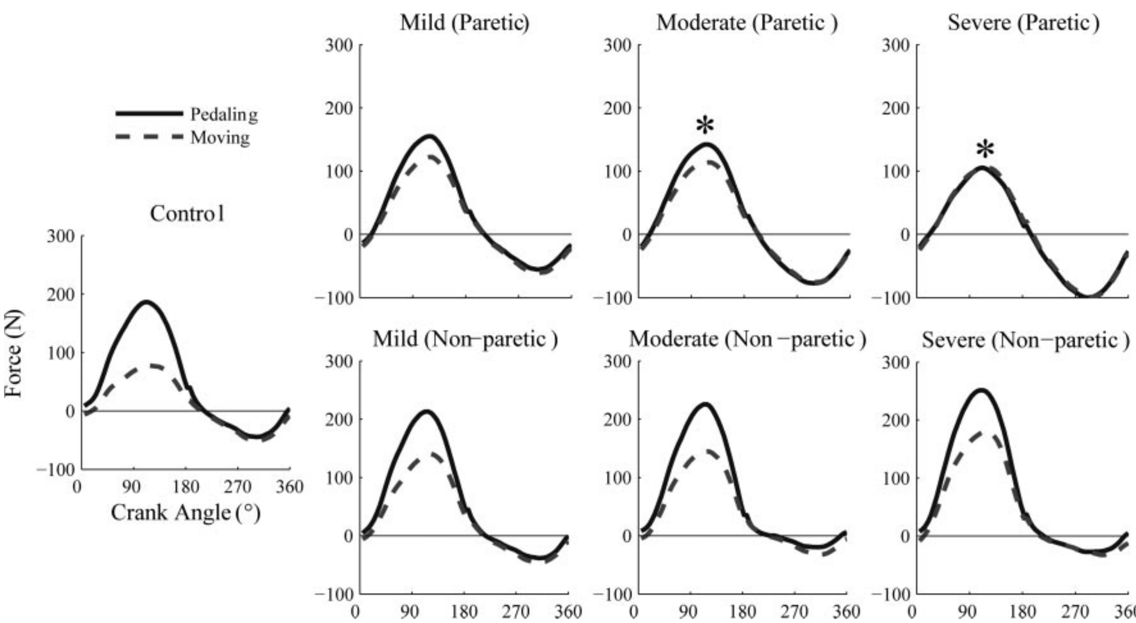

FIG. 6. Comparison of tangential pedal force for pedaling and moving conditions. Because the mechanical work done is proportional to the area under the curve, it is apparent that the output of the paretic and nonparetic leg is substantial during the moving condition and could account for most of the output in subjects with severe hemiparesis. *, mechanical work done was not significantly different ($P < 0.01$).

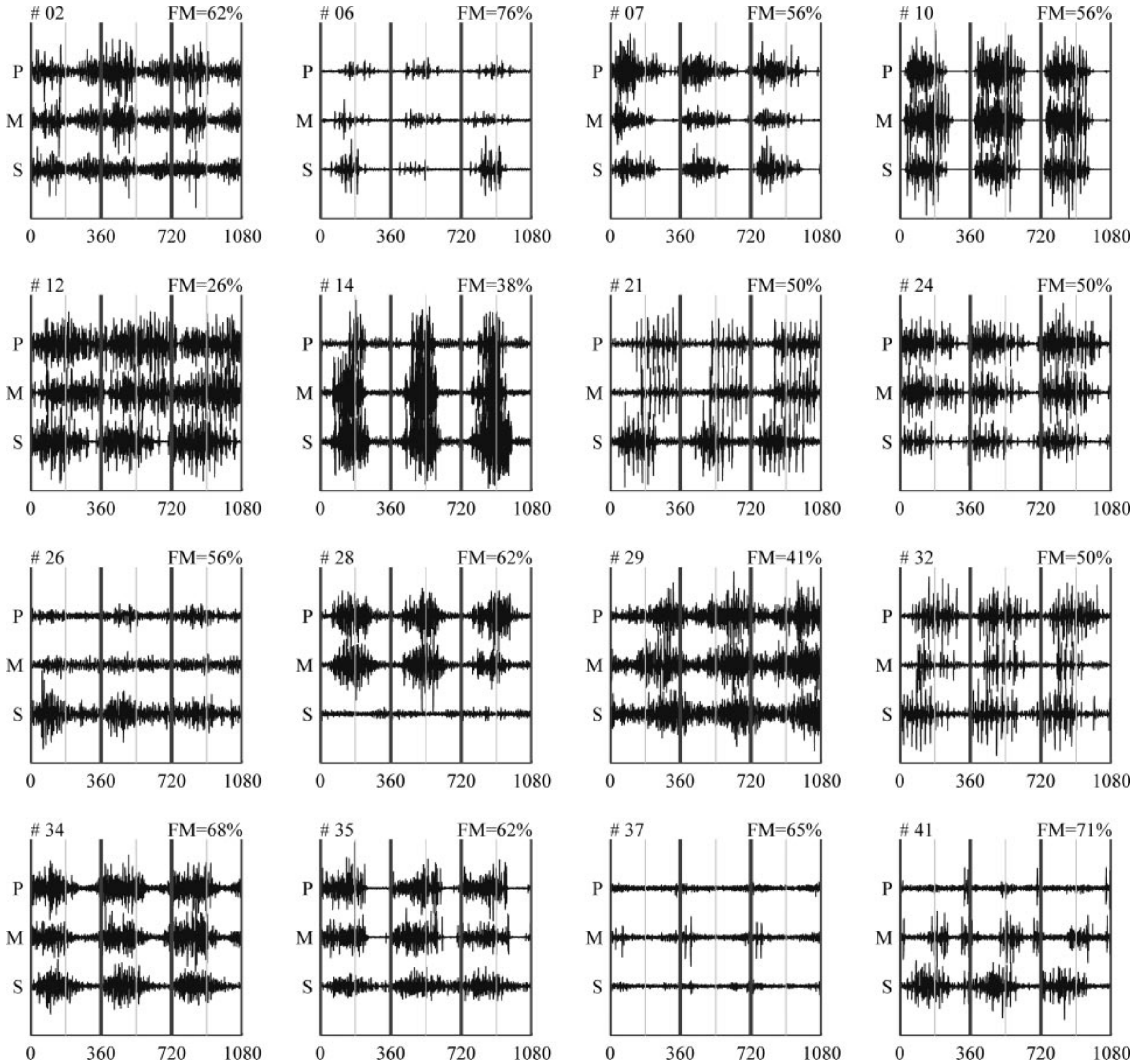

FIG. 7. Individual subject raw data for all individual subjects with severe hemiparesis for 3 consecutive cycles of vastus medialis (VM) activity to compare activity during pedaling (P), moving (M), and stationary (S) conditions. Note that the response tended to be very consistent across conditions in many subjects. The number in the *top left corner* indicates subject number, whereas the number in the *top right corner* indicates that subject's score on the lower-extremity motor portion of the Fugl-Meyer (FM) clinical examination expressed as a percentage.

ingly, we assume that the activity of muscles crossing the ankle was most strongly related to locomotor pattern generation (cf. stretch reflexes). In subjects with severe hemiparesis, however, increased activation was induced in the moving condition in both the paretic and nonparetic legs. Moreover, consistent substantial activation of the ankle muscles was induced in the stationary condition in the nonparetic leg in the severe hemiparesis group and in the paretic leg at all levels of hemiparetic severity. For the muscles contributing to the extension biomechanical function (VM). activation was not induced in the stationary condition, and very low-level activation was induced in the moving condition for control subjects. In hemiparetic subjects, very low-level activation was induced in the nonparetic leg during the stationary condition, and substantial activation was induced in both the paretic and nonparetic legs during the moving condition. In subjects with severe hemiparesis, the stationary condition in the paretic leg produced induced activation of the same magnitude observed during pedaling. In summary, *1*) induced activation similar to that observed in control subjects was observed in all muscles of both legs of hemiparetic subjects in all test conditions: stationary and moving, *2*) muscles that were activated at low levels in control subjects were activated at greater magnitude in both legs of hemiparetic subjects during the moving condition, *3*) induced activation of muscles tended to show greater amplitude as a function of increased hemiparetic severity, and *4*) a complete pattern of rhythmic alternating muscle activity could be induced during the stationary condition in both legs of subjects with severe hemiparesis.

Implications for bilateral organization of locomotor control

Our main results reveal that induced activation of muscles similar to that observed in control subjects was always observed in both legs of hemiparetic subjects. Additionally, muscles that were not activated in control subjects were activated in both legs of hemiparetic subjects during the moving condition, and induced activation of nearly all muscles was greater in subjects with severe hemiparesis than in subjects with mild hemiparesis. Finally, rhythmic alternating muscle activity in all muscles could be induced during the stationary condition in both legs of the severe hemiparesis group. These results establish that, similar to the phenomenon already shown in persons with complete spinal cord injury (Ferris et al. 2004; Kawashima et al. 2005), interlimb pathways may be enhanced in persons with hemiparesis.

One explanation for our results could be that the lesion disrupted the balance of inter-hemispheric activity resulting in loss of inhibition of the excitatory interlimb pathways that are activated by contralateral pedaling. This loss of inhibition would excite ipsilateral muscles (e.g., Jankowska et al. 2003) in both paretic and nonparetic legs in persons with hemiparesis. Under this scenario, disinhibition of excitatory interlimb pathways is more pronounced with increased hemiparetic severity such that contralateral pedaling evokes rhythmic activity more readily. In control subjects, contralateral pedaling showed a different potency for activating muscles contributing to each biomechanical function that depended on ipsilateral sensorimotor activity. The bifunctional thigh muscles—contributing to limb transition functions—were strongly activated by contralateral pedaling, even in the stationary condition with minimal ipsilateral afferent activity. The muscles comprising the plantar-dorsiflexor functions could be activated by contralateral pedaling in the moving condition but were only weakly activated in the stationary condition. This difference was presumably due to the addition of movement-related ipsilateral afferent input. However, the muscles comprising the extensor-flexor functions were only weakly activated, if at all, by contralateral pedaling even in the presence of ipsilateral afferent input during the moving condition. That the nonparetic leg shows increased excitation compared with control legs and that this propensity for activation increases with hemiparetic severity suggests that a common bilaterally organized substrate may be responsible. However, to determine whether there is normally little excitation to ipsilateral extensor muscles due to contralateral pedaling or if separate descending ipsilateral pathways normally act to inhibit the contralateral input, will require directly testing the excitability of the interlimb pathways during various pedaling tasks.

An animal model with clear similarities to our data are the "forelimb inhibition swimming task" test used in rat models of stroke to assess severity of motor impairment. When swimming to a target platform, normal animals hold their forepaws immobile under their chins, bilaterally, as they use their rear paws to paddle through the water (Kolb and Whishaw 1983). However, after lesion via any of five different stroke models, animals always demonstrate marked asymmetry of inter-limb inhibition as revealed by paddling with the impaired (contralesional) forelimb but not with the ipsilesional forelimb (Gonzalez and Kolb 2003). One interpretation of these data is that rhythmic activity of the hind paws induces rhythmic activity in the impaired forepaw that is inhibited under normal supraspinal control. However, postlesion, the ability to inhibit forepaw rhythm is impaired. Although it is presumptive to make direct comparisons between observations in a rat model (2003) and the present data, it is intriguing that in both cases a brain lesion appears to result in enhanced likelihood of inducing rhythmic activity in one limb via rhythmic activity in the other limb(s).

Possible contributing pathways to interlimb excitation

Although disinhibition due to impairment of the descending inhibitory pathway as described about may be a potential explanation for increased interlimb excitation, a potential source of the interlimb excitation is that spinal level coupling of leg pattern generation is enhanced in poststroke hemiparesis. Activation of contralateral muscles could then be modulated by spinal networks activated by ipsilateral leg pattern generation without the need for direct descending input onto the contralateral motoneuron pools. Extensive, bilateral spinal-level interconnections of the pattern generating networks and the bilateral afferent pathways have recently been proposed in reference to pattern generator circuits (Lafreniere-Roula and McCrea 2005). The greater magnitude of induced activation during the moving condition suggests that feedback of ipsilateral movement-related afferent information, likely at the spinal level, plays an important role. Nevertheless, the substantial induced activation displayed by the subjects with severe hemiparesis in the stationary condition suggests that movement related afferent information from the paretic leg is not necessary. Other possible spinal level afferent feedback sources include contralateral movement-related afferent information and bilateral loading related afferent information. Alternatively, the involvement of contralesional descending pathways may also play a role in explaining enhanced interlimb excitation.

The corticoreticular-reticulospinal-spinal interneuronal system (Matsuyama et al. 2004) may provide an avenue for contralesional descending neural pathways to contribute to the paretic motor pattern, providing a second possible source of interlimb excitation. Drew et al. (2004) have presented a conceptual model from cat locomotion data suggesting that bilateral coupling of extension and flexion is facilitated in a phase-dependent context with the same reticulospinal neurons acting to facilitate contralateral flexion and ipsilateral extension or to facilitate ipsilateral flexion and contralateral extension. Dramatic improvements in ipsilateral locomotor function have been observed immediately after spinal cord hemisection in rats. These improvements have been associated with contralateral reticulospinal descending pathways that cross the midline (Fujiki et al. 2004). Similarly, the loss of reticulospinal pathways (e.g., damage to ventral and ventrolateral funiculi of spinal cord) has a severe effect on locomotor function, whereas damage to the corticospinal tract (e.g., dorsal spinal cord hemisection) results in short-lasting changes in overground locomotor function that does not require precise foot placement (Eidelberg et al. 1980). Also in cats, Jankowska et al. (2003) demonstrated that interneuronally mediated actions of reticulospinal neurons were as potent contralaterally (presumably through midlumbar commissural neurons) as ipsilaterally, even though direct actions of reticulospinal neurons were much more potent on ipsilateral motoneurons. Again in cats, a population of excitatory and inhibitory midlumbar commissural interneurons has been identified that project only to contralaterally located neurons (including motoneurons), possibly providing an important avenue for the recruitment of groups of contralateral muscles that subserve a variety of motor synergies (Bannatyne et al. 2003). However, very little is known in humans with hemiparesis about the relative importance of the corticoreticular-reticulospinal-spinal interneuronal system for explaining either coordination deficits or the recovery of hemiparetic locomotion after cerebrovascular lesion (cf., spinal lesions).

Conclusion

Our main results were that contralateral pedaling-induced activation of ipsilateral muscles in both legs of hemiparetic subjects similar to that observed in control subjects during bilateral pedaling. Moreover, muscles that were activated at low levels during the moving condition in control subjects were activated at greater magnitude in both legs of hemiparetic subjects during the moving condition. The greatest magnitude of induced activation was observed in subjects with severe hemiparesis. We suggest that excitatory pathways associated with contralateral pedaling that act on the ipsilateral motor pool in control subjects are disinhibited in both legs in persons with hemiparesis, an effect that is more pronounced with increasing hemiparetic severity. We further suggest that these interlimb pathways are of functional importance in subjects with severe hemiparesis because a complete motor pattern of similar amplitude to the voluntary, bilateral pattern could be activated in the paretic leg by contralateral pedaling in these subjects. Thus interlimb pathways may be responsible for a substantial portion of the paretic leg locomotor output.

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