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Step Trajectory Analysis of Spinal Cord Injured Rats Trained with Neuromuscular Electrical Stimulation Coordinated with Robotic Treadmill Training

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Abstract—**Applying neuromuscular electrical stimulation (NMES) during treadmill training (TT) has been shown to improve functional outcomes, such as gait speed and walking distance, in spinal cord injury (SCI) patients. However, ways to improve this combined NMES+TT therapy have not been investigated. We have developed NMES system for a rodent model of SCI to investigate whether and how more precisely timing the stimulation to robotically assisted hindlimb position might achieve rehabilitation of independent stepping after SCI. In our therapy (NMES+RTT), rodent ankle flexor muscles are stimulated while the hindlimbs are robotically driven through pre-programmed trajectories during treadmill training. The objectives of the work presented here were to quantify changes in step trajectory resulting from our combined NMES+RTT therapy and compare those effects with those induced by robotic treadmill training (RTT) alone.**

Animals were spinally contused to model severe SCI, and either received 2 weeks of NMES+RTT followed by 2 weeks of RTT (n=6) or 2 weeks of RTT followed by 2 weeks of NMES+RTT (n=7). Changes in step trajectories after training were analyzed. According to a deviation measure we developed, the step trajectories improved after either NMES+RTT or RTT training but more closely matched the desired pre-programmed trajectories after NMES+RTT than after RTT only. The step trajectories are also more consistent, as indicated by a coefficient of variation measure, after training and more so after NMES+RTT than after RTT only. These preliminary results from our NMES+RTT vs. RTT study are consistent with the hypothesis that appropriately timing NMES with hindlimb movements during stepping is an effective therapy for restoring the ability to step after spinal cord injury.

I. Introduction

Neuromuscular electrical stimulation (NMES)[1] and weight-supported treadmill training [2] are two therapies which have demonstrated promise for rehabilitation of walking in spinal cord injury (SCI). The functional outcome resulting from application of NMES in combination with RTT has been assessed in a number of clinical studies[3, 4].In particular, applying NMES to the nerves which flex the ankle during treadmill stepping has shown to improve gait speed and walking distance. However, the timing of the stimulation is only approximated to occur during a certain portion of the swing phase of the gait cycle. Ways to improve this combined NMES+WSTT therapy have not been investigated. We hypothesize that timing stimulation more precisely to hindlimb position during stepping would improve those outcomes by exploiting spinal plasticity[5]. We have been developing an NMES system which times the stimulation to robotically assisted hindlimb position for a rodent model of SCI in order to test this hypothesis.

Some evidence exists that treadmill training alone can enhance spinal cord circuits which are responsible for producing locomotion [6-9]. A critical factor in this capability to encourage spinal plasticity appears to be the afferent activity produced during the stepping [6, 10, 11]. In this scenario, the coordination of applied stimulation with the afferent feedback generated during stepping would be essential. We are attempting to develop our NMES therapy to time stimulation to such afferent feedback by utilizing the capabilities of robotic treadmill training by which the hindlimbs are guided through pre-programmed step trajectories and the actual hindlimb position is continuously sensed.

RTT alone has been shown to improve stepping in spinal cord injured animals [9, 12]. We have conducted a study to compare the effects of our combined NMES+RTT therapy with RTT alone. The objectives of the work presented here were to quantify changes in step trajectory resulting from NMES+RTT therapy and compare those effects with those induced by RTT alone.

II. Methods

A. Animal experiments

Female Sprague-Dawley rats were given severe spinal cord injury, and a pair of recording and stimulating electrodes was implanted in the tibialis anterior (TA) ankle flexor muscle of each hindlimb. Surgical procedures for spinal contusion and electrode implants are described in detail in [13]. Fourteen rats survived the surgeries and completed training. Eight of those rats (Group 1) received 2 weeks of RTT only followed by NMES+RTT, while six rats (Group 2) received therapies in the reverse order.

To perform RTT, robotic arms are attached to the ankles. The treadmill moves at 6cm/s while a weight-support boom supports 85% of the rat's weight. The robot arms impose feedback-controlled (proportional-integral-derivative control) forces to attempt to keep the hindlimbsmoving along

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a pre-programmed trajectory (Fig. 1, dash-dot gray trace). The robot control was made more flexible over the two-week course of RTT, so that by the end of training, forces were only imposed if the ankle deviated more than 1cm from the pre-programmed robot trajectory. For NMES+RTT therapy, stimulation was applied first 50 % of the swing phase, as described in [5]. However, if the rat's ankle position did not follow the programmed pattern sufficiently, as defined by the correlation coefficient between desired and actual trajectory in the past 50ms, then the stimulation was aborted. Stimulation was delivered to the TA at the following parameters: 70pps, 100μs pulse width, and 1.5 times the animal's motor threshold.

Baseline testing was performed after rats had approximately 3 weeks to recover from spinal cord injury. Testing was performed again after the first two weeks of training and after the subsequent two weeks of testing (a total of 4 weeks after the baseline testing). During testing, rats received neither electrical stimulation nor robotic assistance.

B. Trajectory Analysis

Deviation (δ) of the rat's step trajectory from the pre-programmedtrajectory, along which the ankle was robotically guided, was calculated for each test point, at baseline, two-weeks, and 4-weeks,according to (1) and (2).

$$\delta[i,j] = \sqrt{(x[i,j] - x_r[i,j])^2 + (y[i,j] - y_r[i,j])^2} \quad (1)$$

$$\delta = \frac{1}{N}\sum_{j=1}^{N}\frac{1}{D}\sum_{i=1}^{D}\delta[i,j], \quad (2)$$

where*x[i,j]* and *y[i,j]* are the Cartesian coordinates of the actual ankle position which is continuously sensed by the robot at time index *i* during the j^{th} detected step; x_r and y_r are the coordinates of the pre-programmed trajectory imposed by the robot (Fig. 2); *N* is the number of steps during the given test period; and *D* is the step duration in number of samples. Steps were defined as starting at toe-off and ending at the next toe-off, and detected by finding minima in *x*. The portion of the position signals between each *x* minima was considered a step if the rat's horizontal displacement during that period reached at least a minimum threshold distance of 5 mm; we have observed that otherwise, any movement with a smaller displacementwas not likely a deliberate step forward. This step detection method was verified against video recordings recorded during testing. Each detected step was normalized in time by linearly interpolating between points so that each of the points in the step could be compared against a corresponding sample in the imposed robot trajectory. Furthermore, to ensure that corresponding phases of the gait cycle were being compared in the deviation computation, before performing the interpolation, the steps were time-normalized in three phases, into which each step was divided: "upswing" (from toe-off to peak height, or maximum *y*), "downswing" (from peak height to paw contact, or maximum *x*), and "stance" (from paw contact to toe-off).

A couple limitations were found with this absolute deviation measure. For example, trajectories that could be assessed visually as qualitatively good steps, and seemed to match the shape of the pre-programmed robot trajectory

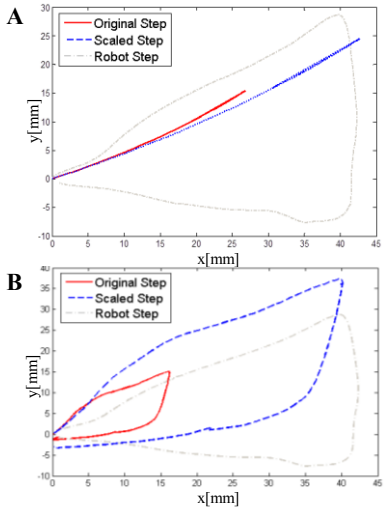

Figure 1. The scaling applied according to (4)-(6) yields a measure which is consistent with a visual assessment of step quality. One example of a step which poorly matches the robot trajectory (A) but has a lower deviation before scaling (δ = 19.3 before scaling,δ_G= 53.0 after scaling) than a step which better matches the robot trajectory (B) but has a high deviation before scaling (δ = 23.0,δ_G = 17.9).

relatively well, sometimes yielded larger deviation values than steps which could be visually assessed as steps which poorly matched the shape of the reference trajectory. This discrepancy could generally be explained because the "good" steps were offset from the robotically imposed steps and/or the shape of the step might have better matched the desired robot trajectory but the rat did not extend its hindlimb as far as the extent of the robot trajectory, as can be seen in Fig. 1.

To correct for this problem, the trajectories were offset so that all steps had the same origin as the robot trajectory and were scaled such that the "extent" of each rat's step equaled the "extent" of the desired robot trajectory. "Extent" of a step is defined as the distance from the origin to the farthest point in the step. In other words, the rat's coordinates were then offset to have the same origin as the robot trajectory (3) and for each step, a gain was calculated according to (4), where *D*is the extent of the rat's step, and D_r is the extent of the desired robot step. The rat's coordinates were then scaled by that gain factor before computing the scaled deviation, as shown in (5). However, to take into account that a step that, without scaling, has a similar extent to the robot trajectory is still better than a step with the same shape but has a smaller extent than the robot trajectory, the final deviation measure used in these analysis factored in the gain used to scale the rat trajectory (6).

$$x' = x - \min(x)$$
$$y' = y - \min(y), \quad (3)$$

$$G = \frac{\max\left(D_r\right)}{\max\left(D\right)}, \tag{4}$$

$$\delta_s[i,j] = \sqrt{(Gx'[i,j] - x_r[i,j])^2 + (Gy'[i,j] - y_r[i,j])^2} \tag{5}$$

$$\delta_G = G\delta_s, \tag{6}$$

Variability in stepping was also measured by computing the coefficient of variation of the *x* coordinates and *y* coordinates during each test (7), but data points from two of the rats were removed because fewer than five steps were completed during the test period.

$$CV_x = \frac{\sigma_x}{\bar{x}}, CV_y = \frac{\sigma_y}{\bar{y}} \tag{7}$$

III. Results

Examples of the trajectory for a rat from group 1 and one from group 2 at each of the testing time points are shown in Fig. 2. The step trajectory of the group 1 rat did not improve much after two weeks of RTT, but the trajectory became more consistent and better matched the robot trajectory after a subsequent 2 weeks of NMES+RTT. The trajectory of the group 2 rat improved dramatically after 2 weeks of NMES+RTT, in terms of deviation from the robot trajectory and decreased variability in stepping, whereas after a subsequent two weeks of RTT only, the step trajectories seemed to return to baseline quality of stepping.

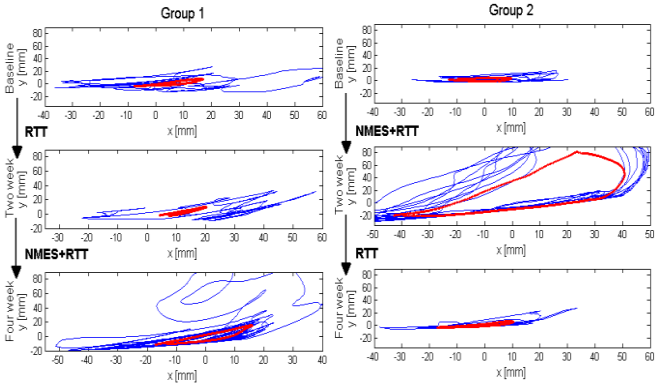

Figure 2. Step trajectory for a rat from Group 1at baseline (without any training), after two weeks of RTT, and aftertwo weeks of NMES+RTT; similarly for a Group 2 rat, except order of NMES+RTT and RTT are reveresed. Bold red trace shows average trajectory; lighter blue traces show trajectory of individual steps.

According to the deviation measure, hindlimb trajectory generally improved (decreasing δ_G) after NMES+RTT but worsened (increasing δ_G) after RTT only (Fig. 3).This was true whether NMES+RTT was applied before or after RTT. In group 1, after 2 weeks of RTT, the deviation increased on average by 26.0%, relative to baseline values, whereas it decreased by 24.3% after 2 weeks of NMES+RTT. In group 2, the deviation decreased on average by 36.6% after 2 weeks of NMES+RTT and then increased 45.1% after an additional 2 weeks of RTT only. This trend can be visualized in Fig. 4, which shows the spread of percent

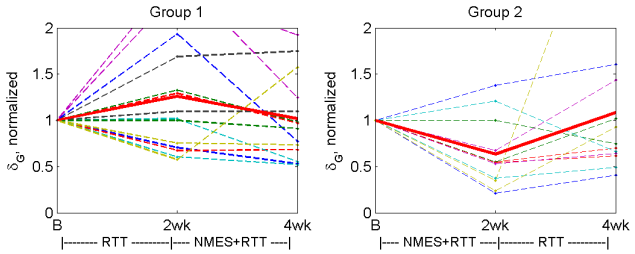

Figure 3. Deviation, normalized to baseline values, for each rat (dashed lines) at baseline, after the 1st 2 weeks of training, and after the final 2 weeks of training. The solid bold trace shows the group average.

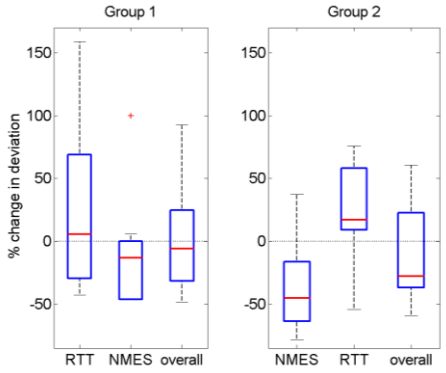

Figure 4. Percent change in the deviation measure ($\Delta\delta_G$), relative to baseline values from baseline to 2 weeks, 2 weeks to 4 weeks, and from baseline to 4 weeks. Thus, for Group 1, the first box-and-whisker plot shows the percent change afte r 2 weeks of RTT, the second after a subsequent 2 weeks of NMES+RTT, and the last shows the overall change after the total 4 weeks of training. Box extends from 25th to 75th percentiles, solid line inside the box marks the median, and whiskers extend to the ranges of the data that are not considered outliers. Outliers are marked by a cross.

change in deviation values after 2 weeks of RTT only, 2 weeks of NMES+RTT, and after the total 4 weeks of training. The percent change is generally negative after NMES+RTT generally positive after RTT only; and any improvements gained by NMES+RTT seemed to be cancelled by aggravation caused by RTT, reflected by the percent change from baseline to 4 weeks total training generally spanning the $\Delta\delta_G$ =0 line (also see Table 1, baseline to 4 week differences). Only the difference from baseline to two weeks, after NMES+RTT training, in group 2 were significant (paired t-test, p = .012), but the 90% confidence intervals for the differences between the time points are shown in Table 1.

TABLE I. Changes in Deviation with Training

	90% Confidence Interval for $\Delta\delta_G$		
	2wk - B	***4wk – 2wk***	***4wk – 2wk***
Group 1	[-3.7 : 13.5]	[-14.8 : 1.1]	[-9.7 : 5.9]
Group 2	[-34.5 : -8.6]	[-1.6 : 42.5]	[-23.7 : 21.9]

In addition to these changes in deviation after training, we also noticed the rats stepped more consistently after

NMES+RTT (Fig. 2, Group 1 rat from 2 weeks to 4 weeks; Group 2 rat from baseline to 2 weeks). The progression of CV_x and CV_y from baseline to two weeks to fourweeks (Fig. 5) indicates that this was the case more generally across rats. Variability in both x and y during stepping improved (decreased) on average after NMES+RTT but worsened (increased) after RTT only.

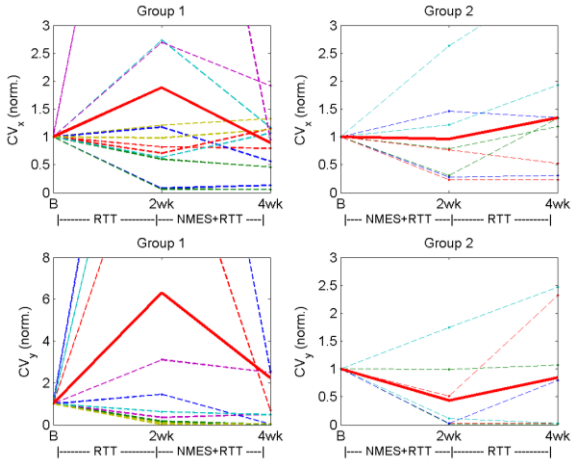

Figure 5. Variability in step trajectory was measured by coefficient of variation, normalized to baseline values, in the x and y dimensions. CV_x and $CV_y$are shown for each rat (dashed lines) at baseline, after the 1st 2 weeks of training, and after the final 2 weeks of training. The solid bold trace shows the group average.

IV. Discussion

We have developed and applied a deviation measure to assess step trajectories to spinal cord injured rodents who received our neuromuscular electrical stimulation therapy timed to robotically controlled stepping (NMES+RTT), and compared changes in deviation after NMES+RTT with changes after RTT only. The hindlimb trajectory appears to more closely follow the trajectory imposed during trainingafterNMES+RTT; whereas, applying RTT alone, at the levels of robotic assistance used in this study, appears to disrupt motor control of hindlimb stepping. This is consistent with findings from[12], which showed that providing low levels of assistance was more beneficial to rehabilitating stepping than rigid robotic control, and that the latter could actually suppress rehabilitation of stepping. According to the CV measures, rats stepped more consistently after NMES+RTT but less consistently after RTT.These observations together may indicate that while robotic assistance alone suppresses motor learning, NMES+RTT encourages it.

Our NMES+RTT therapy is being designed in attempt to encourage synaptic potentiation by pairing electrically induced activity with treadmill training induced sensory activity, and thereby promote rehabilitation of stepping through improved spinal circuit control. Although we do not have evidence to show that this is the mechanism by which improvements in step trajectory were achieved, the results are consistent with the notion that if the spinal circuitry is actively engaged in producing movements during training, then motor learning will be encouraged, whereas robotic assistance alone essentially encourages passive movements during training, such that when the assistance is taken away, the rat is no better able to produce steps independently than before training[10]. A more complete analysis of our data including changes in EMG activation patterns and changes in immunohistochemical markers of synaptic plasticity and corresponding kinematic measures such as step length, height, and speed, is forthcoming and should help to answer some of these questions about whether and how NMES+RTT encourages motor learning.

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