Neural control of balance in increasingly difficult standing tasks

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Chapter 2

Increasing mediolateral standing sway is associated with increasing corticospinal excitability, and decreasing M1 inhibition and facilitation

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ABSTRACT

In standing, corticospinal excitability increases and primary motor cortex (M1) inhibition decreases in response to anterior posterior or direction unspecific manipulations that increase task difficulty. However, mediolateral (ML) sway control requires greater active neural involvement. Therefore, the primary purpose of this study was to determine the pattern of change in neural excitability when ML postural task difficulty is manipulated and to test whether the neural excitability is proportional to ML sway magnitude across conditions. Tibialis anterior corticospinal excitability was quantified using motor evoked potential (MEP) and postural sway was indexed using ML center of pressure (COP) velocity. Additionally, we examined inhibition and facilitation processes in the primary motor cortex using the paired pulse short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) techniques respectively. Measurements were repeated in four conditions with quiet stance as a control. Differences between conditions were tested using one-way repeated measures ANOVAs, on log transformed data. Associations were quantified using Spearman’s Rank Correlation Coefficient. There was a significant main effect of condition on all the neural excitability measures with MEP (p < 0.001) being highest in the most difficult condition, and SICI (p = 0.01), ICF (p < 0.001) being lowest in the most difficult condition. Increasing ML COP velocity was significantly associated with increasing MEP amplitude (rho = 0.68, p < 0.001), but decreasing SICI (rho = 0.24, p =0.03) and ICF (rho = −0.54, p < 0.001). Our results show that both corticospinal and M1 excitability in standing are scaled in proportion to ML task difficulty.
1. INTRODUCTION

During unperturbed standing, the body’s center of mass (COM) sways spontaneously, but remains within the base of support (BOS) as active and passive mechanisms generate appropriate counteractive forces and regulate the center of pressure (COP) path. Within limits, COP movements during quiet standing and larger fluctuations induced by decreasing the BOS size are considered normal in healthy adults [1–3]. However, excessive COP movements, especially in the mediolateral (ML) direction, predict falls in old adults [4–6] and are characteristic of individuals with Parkinson’s disease [7] and cerebellar deficits [8]. Also, modulation of both voltage and time-frequency based EEG measures is more pronounced during ML compared to AP sway [9]. Therefore, it is clear that AP and ML sway components are controlled using independent strategies [10] and ML control likely requires greater neural resources [9]. However, studies examining neural excitability in standing have employed manipulations only in the AP direction or without directional specificity [11–15]. Therefore, in this study we examined neural excitability changes in response to manipulation of ML difficulty indexed using COP movements.

While segmental inputs to postural control are well established [14,15], there is now evidence that the primary motor cortex (M1) also contributes to the control of sway during unperturbed, quiet standing [11,13,16] and more complex postural tasks [17–19]. Transcranial magnetic stimulation (TMS) studies demonstrate that when experimental manipulations increase COP movements in standing, corticospinal excitability (CSE) increases and M1 inhibition decreases [11–13]. The overall increase in excitability can drive muscle activation and thereby create greater forces to counteract COM movements. CSE is a net outcome of multiple inhibitory and facilitatory neurophysiological processes, at various anatomical locations and an increase could be mediated by alteration in spinal excitability. The decrease in M1 inhibition provides more convincing evidence for cortical involvement in postural control. Therefore, in this study we examined two cortex specific measures of excitability, along with CSE. Also, it is unclear whether neural excitability is scaled in proportion to the magnitude of sway. Moderate correlations between AP or resultant COP movements, and H-reflex [15] or M1 inhibition [11] have been reported in older adults, but not in young.

We measured neural excitability using TMS and manipulated ML sway by altering the BOS and/or foot support, in young adults. Preliminary work confirmed that the selected manipulations systematically increased ML COP velocity, indicating an increase in difficulty. We tested the tibialis anterior (TA) because it is a primary ankle invertor which is essential for maintenance of ML balance. In fact, its contribution to ML control increases as BOS decreases [3,10,20]. The primary purpose of this study was to determine TA neural excit-
ability in four standing conditions with increasing ML COP velocity, and to test whether excitability is correlated with COP velocity. We hypothesized that an increase in task difficulty would lead to increase in CSE and M1 facilitation and decrease in M1 inhibition, in proportion to the increase in ML COP velocity.

2. EXPERIMENTAL PROCEDURES

2.1. Participants
Healthy adults (Age: 25.7 ± 4.2 years; 11 females, 9 males) volunteered to participate in the study. Three individuals were unable to complete the entire data collection due to fatigue and/or discomfort from prolonged stimulation. The number of participants included in each analysis is indicated in the tables and figures. Participants were excluded if they reported ongoing symptoms due to lower extremity injury, a history of neurological disorders, seizures, head trauma or unexplained loss of consciousness; or if they were pregnant; had metal implants or pacemakers; used medication known to lower seizure threshold or had blood relatives with a history of seizures. Written informed consent was obtained and all procedures were conducted in accordance with the Declaration of Helsinki. The study was approved by the Institutional Review Board of the University of Southern California, Health Sciences Campus. Foot dominance was determined using a 3-question inventory [21].

2.2. Data acquisition
Electromyographic (EMG) signals were recorded from the dominant-side TA using a bipolar surface electrode (radius 12 mm, inter electrode distance 17 mm, Motion Lab Systems, Baton Rouge, LA) which was aligned parallel to the muscle fibers and placed over the bulk of the muscle belly, located by palpating during voluntary contraction. The ground electrode was placed on the anterior tibial surface. Data were acquired at 15 kHz in order to simultaneously capture the TMS pulse, and stored using Signal software (Signal v6, Cambridge Electronic Design Ltd, Cambridge UK). COP data were sampled at 1.5 kHz using AMTI force platforms (Model #OR6-6-1, Watertown, MA) embedded into the laboratory floor. Data were acquired and stored using Qualisys software (Qualisys Inc., Gothenburg, Sweden).

TMS pulses were delivered using a double cone coil (110 mm) connected to a BiStim module (The Magstim Co., Whitland, UK) and two single-pulse magnetic stimulators (Magstim Model 2002). A lycra cap marked with a 1 cm grid ensured consistent manual coil positioning, and the current was directed posterior-to-anterior. The hotspot was defined as the location where the largest and most consistent motor evoked potentials (MEP) were obtained, and was located over the midline or 1–2 cm lateral in all participants. Active motor threshold (MT) was determined in standing by systematically varying the stimulation
intensity to find the lowest stimulator output at which 3 out of 5 MEPs had peak-to-peak amplitude of at least 100 µV [11]. The average threshold was 56 ± 13% of maximal stimulator output. For measuring short interval intracortical inhibition (SICI) and intracortical facilitation (ICF), a subthreshold (80% MT) conditioning pulse was applied followed by a supra-threshold (120% MT) test pulse, separated by inter-stimulus intervals (ISI) of 3 and 13 ms respectively. Ten paired pulses each for SICI and ICF protocols, and 10 single pulses at 120% MT were applied in random order, with a minimum of 5 s between stimuli.

2.3. Procedures

All data were acquired during a 2.5 h long lab visit. In pilot testing we examined several methods for eliciting TA maximal voluntary contraction (MVC) – isometric dorsiflexion and inversion with manual resistance in standing and sitting; participants standing on one foot with heel resting on the support surface, hands rested on a stable surface for balance and instructed to “raise their toes as high as possible” for 3 s. Participants inverted and dorsiflexed the foot during the latter and MVC was consistently higher than that obtained using the former. The procedure was repeated 3 times.

TMS and COP measurements were acquired with participants standing on a force plate. Four postural conditions were examined (listed from least to greatest postural difficulty): 1) Standing on 2 feet, feet shoulder width apart (i.e., wide base; 2WB); 2) Standing on 2 feet, feet as close together as possible (i.e., narrow base; 2NB); 3) Standing with dominant foot on the floor (stance limb) and other foot on a solid block, ~30 cm high (1Step), and 4) Standing with dominant foot on the floor (stance limb) and other foot on an unstable spring (stiffness – 49.04 N/cm), ~30 cm high (1Spring) (Fig. 1). Post-hoc analysis confirmed that in 1Step and 1Spring, majority of the body weight i.e. 90.7 ± 3.6 and 94.5 ± 2.2% respectively was supported on the stance limb. The order of conditions was randomized.

**Figure 1** Four conditions were used to manipulate mediolateral center of pressure (ML COP) velocity: A) wide base with feet shoulder width apart (quiet stance; 2WB); B) narrow base condition with feet as close together as possible (2NB); C) one foot supported on a stable block with >80% body weight on lower, dominant foot (1Step); D) one foot supported on an unstable spring with >80% body weight on lower, dominant foot (1Spring).
across participants, with 3–5 min of rest between conditions. For 2WB, the foot position was marked and maintained throughout testing. Participants were verbally instructed to stand as still as possible.

### 2.4. Data analysis

EMG and COP data were processed using custom Matlab (The Mathworks, Natick, MA) codes. EMG data were down-sampled to 3.0 kHz, bandpass filtered using a 4th order Butterworth filter with 10 Hz and 1 kHz low pass and high pass cut off respectively, and rectified. We estimated background EMG (bEMG) from the mean voltage measured in a 100 ms window before the TMS stimulation artifact. For MVC trials, moving average with a 100 ms window was used to smooth the data, the peak was measured and the highest of 3 trials was selected.

COP data were filtered using a 4th order low pass Butterworth filter with 10 Hz cut off. ML velocity was calculated in a 2 s window before each TMS pulse, and averaged across windows to obtain a single estimate for each condition. Velocity was selected because it is predictive of falls [5,22] and more reliable than amplitude or area based measures [23,24]. Post-hoc analysis determined that participants were swaying laterally in the 1 s preceding TMS pulse application in approximately half the trials – 55 ± 10, 55 ± 7, 57 ± 9 and 55 ± 7% in 2WB, 2NB, 1Step and 1Spring respectively. Finally, directional bias of the manipulations was confirmed by comparing AP and ML COP velocity. The percentage increase from 2WB to 1Spring was much higher for ML (293%) than AP (203%) velocity.

Initial processing of the TMS data was done using Signal software (Signal v6, Cambridge Electronic Design Ltd, Cambridge UK). In each trial, the MEP amplitude was defined as the peak to peak voltage within a 25–65 ms window after application of the magnetic pulse. Visual inspection was used to ensure that the MEP was within this window. Subsequent processing was performed using Matlab (The Mathworks, Natick, MA). Peak to peak amplitudes from 10 single or paired pulse trials were averaged to estimate the test and conditioned MEPs respectively. The test MEP amplitude was used as an index of CSE. The following formulae were used to quantify SICI and ICF, using MEPs averaged over 10 trials –

1. $\text{SICI} = \frac{(\text{ConditionedSICI/Test MEP} \times 100)}{;}$ smaller values indicate greater inhibition.
2. $\text{ICF} = \frac{(\text{ConditionedICF/Test MEP} \times 100)}{;}$ higher values indicate greater facilitation.

### 2.5. Statistical analyses

SPSS (Version 22, IBM Corp., Armonk, NY) software was used. When the Shapiro-Wilk test revealed that variables were not normally distributed in one or more conditions, values were log transformed for the ANOVA. Five one-way univariate ANOVAs, with condition as
a fixed factor, were used to test for effect of condition on bEMG, COP velocity, MEP, SICI and ICF. When the F test was significant, pairwise differences were tested using Tukey’s post hoc comparisons. Linear regression analyses with condition and bEMG as independent variables was used to test whether bEMG predicts MEP, SICI and ICF, in addition to condition. Spearman’s correlation coefficient was used to test for the associations between COP velocity and TMS measures, with data pooled across the four conditions. Curve fitting was applied to determine whether the variance in the data was better explained by linear or quadratic association. The significance level was set at 0.05.

3. RESULTS

3.1. ML COP velocity

Main effect of condition on velocity (p < 0.001) was significant. Velocity in all conditions was significantly higher than 2WB (p < 0.05, Table 1), with highest velocity in 1Spring.

3.2. bEMG and TMS measures

Main effect of condition on bEMG (p < 0.001), MEP (p < 0.001), SICI (p= 0.01) and ICF (p < 0.001) was significant. In the most difficult condition – 1Spring, bEMG and MEP amplitude were highest, SICI and ICF were lowest (Table 1). Regression analyses revealed that condition was a significant predictor of MEP (p < 0.001), SICI (p= 0.04) and ICF (p= 0.03), while bEMG was a significant predictor of ICF (p =0.02) but not MEP (p = 0.72) and SICI (p= 0.21). MVC values were 0.36 ± 0.13 mV.

Table 1 Mediolateral center of pressure (ML COP) velocity, background EMG (bEMG), motor evoked potential (MEP), short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) in each condition: mean ± standard deviation.

<table>
<thead>
<tr>
<th></th>
<th>F-value</th>
<th>2WB</th>
<th>2NB</th>
<th>1Step</th>
<th>1Spring</th>
</tr>
</thead>
<tbody>
<tr>
<td>bEMG</td>
<td>13.72</td>
<td>2.91 ± 1.19</td>
<td>3.34 ± 1.81%</td>
<td>4.27 ± 2.12*</td>
<td>6.47 ± 2.31*</td>
</tr>
<tr>
<td>ML COP velocity (cm/s)</td>
<td>81.92</td>
<td>0.43 ± 0.12 (n=20)</td>
<td>0.63 ± 0.12* (n=20)</td>
<td>0.80 ± 0.37* (n=19)</td>
<td>1.69 ± 0.43* (n=19)</td>
</tr>
<tr>
<td>MEP (mV)</td>
<td>19.12</td>
<td>0.39 ± 0.20 (n=20)</td>
<td>0.56 ± 0.29 (n=20)</td>
<td>0.83 ± 0.40* (n=19)</td>
<td>1.14 ± 0.46* (n=19)</td>
</tr>
<tr>
<td>SICI (%)</td>
<td>4.63</td>
<td>58.42 ± 25.51 (n=20)</td>
<td>59.51 ± 15.69 (n=20)</td>
<td>66.40 ± 15.25 (n=19)</td>
<td>75.13 ± 17.79* (n=19)</td>
</tr>
<tr>
<td>ICF (%)</td>
<td>6.73</td>
<td>196.66 ± 110.60 (n=19)</td>
<td>171.33 ± 69.46 (n=19)</td>
<td>127.86 ± 22.73* (n=18)</td>
<td>116.95 ± 17.32* (n=17)</td>
</tr>
</tbody>
</table>

* indicates significantly different from 2WB using post-hoc Tukey's test (p<0.05)
ML COP velocity was significantly linearly correlated with MEP (p < 0.001, \( \rho = 0.68 \)), SICI (p= 0.03, \( \rho = 0.24 \)) and ICF (p < 0.001, \( \rho = -0.54 \)) (Fig. 2). The association between ML COP velocity and SICI was best explained by a linear fit, while the associations with MEP and ICF were better explained by a quadratic fit. For MEP, quadratic (\( R^2 =0.39, p < 0.001 \)) and linear (\( R^2 =0.35, p < 0.001 \)) fits explained a similar percentage of variance. However, for ICF the quadratic fit (\( R^2 = 0.25, p < 0.001 \)) explained a higher percentage of variance than the linear (\( R^2 =0.15, p = 0.001 \)) fit.

**Figure 2** Correlations between neural excitability and mediolateral center of pressure (ML COP) velocity; A) motor evoked potential - ML COP velocity (p<0.001); B) short interval intracortical inhibition - ML COP velocity (p=0.03); C) intracortical facilitation - ML COP velocity (p<0.001)
4. DISCUSSION

In partial agreement with our hypothesis, TA CSE increased and M1 inhibition decreased when postural task difficulty was manipulated by altering the BOS and foot support, in standing. Contrary to our expectation, M1 facilitation also decreased with increase in task difficulty. All three measures of neural excitability were correlated with ML COP velocity – i.e. excitability was scaled in proportion to postural sway.

4.1. Increase in CSE, decrease in M1 inhibition and facilitation as standing task difficulty increases

Independent of the direction of manipulation, reports suggest a consistent pattern of increasing CSE and decreasing M1 inhibition as postural task difficulty increases [11–13]. However, there are conflicting reports regarding M1 facilitation – ICF is lower in standing compared to sitting [16], but similar across conditions when sensory feedback or anterior trunk support are manipulated in standing [11,12]. As difficulty increases, greater internal forces must be generated so that COP shifts are sufficient and appropriate to ensure that the COM remains within the BOS. Theoretically, this can be achieved by increasing neural excitability. Therefore, our finding of simultaneous decrease in M1 inhibition and facilitation presents a conundrum. Specifically, the decrease in facilitation appears to be counterproductive to the overall goal of increasing CSE. Parallel changes in excitatory and inhibitory activity have previously been observed in the upper extremity during the preparatory phase of reaction time tasks [25,26]. It has been proposed that these competing processes ensure that neural excitability is suitable for executing appropriate motor patterns, while inappropriate movements are withheld [27]. In other words, each neurophysiological process plays a distinct role which is essential for successfully achieving the task goal. We propose that a similar principle applies to postural control – i.e. in difficult conditions low inhibition can increase TA activation and ensure that the mechanical demands of the posture are satisfied. Additionally, it ensures that the TA is ready to be activated in case of a perturbation. On the other hand, low facilitation prevents unnecessary muscle activity that could interfere with ongoing maintenance of balance. This becomes more critical when difficulty increases and inadvertent muscle activity could create self-generated perturbations with the potential to compromise balance. However, as evidenced by the quadratic association, ICF plateaus when difficulty exceeds a certain threshold. It is possible that in the most difficult postures the need to maintain high CSE outweighs the need to be cautious and prevent movement. This may explain why some postural control studies found changes in SICI without concurrent changes in ICF, depending on the conditions employed in a specific study.
4.2. Correlations between COP velocity and neural excitability

In line with the previously reported weak or insignificant correlations between AP COP and H-reflex, MEP or SICI in young adults [11,15,28], we found statistically significant but low to moderate strength associations between neural excitability and ML COP velocity. Though bEMG differed between conditions, regression analysis revealed that bEMG was a significant predictor only for ICF. Our initial hypothesis was based on the assumption that neural excitability determines the level of muscle activation which in turn drives COP adjustments. However, given that condition is a significant predictor of MEP and SICI, but bEMG is not, we hypothesize that TA excitability changes serve other roles, in addition to increasing ongoing contraction and COP movements.

Neural excitability changes without concomitant changes in muscle contraction [29,30], can reflect subliminal or subthreshold increases in excitability that prepares muscles for context-specific activation, but does not influence ongoing contraction. We hypothesize that the changes in TA excitability ensure that it is appropriate for the new context where perturbations pose a higher risk, and not for the sole purpose of influencing COP movements. Though not intended as such, in our study, the TMS pulses constituted a mechanical perturbation which was expected, but had unpredictable temporal spacing. Since participants were explicitly instructed to stay as still as possible, it is likely that the motor control system initiated measures to prepare for the perturbation in advance. Additionally, in the context of postural control, there is an inherent instinct to avoid a fall and potential injury. Previous studies compared conditions in which a TMS pulse [31,32] or mechanical change [33,34] induced a perturbation and participants were instructed to either assist/disregard or resist it. In agreement with our study, CSE increased and M1 inhibition decreased when participants were asked to resist the perturbation. The simultaneous decrease in SICI and ICF also reinforces the hypothesis that M1 excitability in more difficult conditions is aimed at achieving various motor goals, besides maintaining COP movements. Both increasing COP movements to minimize COM movements, and preparing to respond to external perturbations require an increase in neural excitability. On the other hand, excessive excitability poses a risk of creating self-initiated perturbations. Therefore, the different neurophysiological processes must be optimally co-varied for effective postural control.

4.3. Limitations

It has been reported that TA MEPs are smaller during forward compared to backward sway [13] and it is possible that excitability differs between medial and lateral sway. In our study, the proportion of trials with medial and lateral sway were approximately equal in all conditions. Controlling for sway direction is likely to decrease inter-trial variability within each condition and may even amplify the differences between conditions.
A limitation of using TMS to study postural control is that the coil could have a stabilizing effect and consequently affect neural excitability. Indeed, in a subset of participants we found higher COP velocity without the coil and addressed this issue by using velocity measured with the coil for all analyses.

The parallel decrease in SICI and ICF, despite low bEMG suggests that TA neural excitability is modulated in preparation for perturbations or a potential loss of balance, rather than for ongoing sway control. Though the TMS pulse acted as a perturbation, we were unable to quantify and comment on the quality of the biomechanical response. Therefore, direct behavioral consequences of the changes in excitability remain unclear. Further investigations are required to determine whether this pattern of covariation in SICI and ICF translates into better postural performance and response to perturbations.

5. CONCLUSIONS

Our study demonstrates that TA CSE increases, and M1 inhibition and facilitation decrease in proportion to ML COP velocity when postural task difficulty increases in standing. It confirms that the general pattern of neural excitability modulation is consistent across AP and ML postural manipulations. Additionally, it adds to the limited evidence that in standing a part of the variability in neural excitability is explained by postural sway magnitude.
6. REFERENCES


