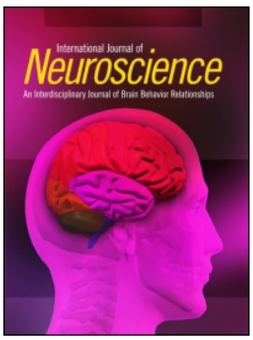

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The relationship between the sensory responses to ankle-joint loading and corticomotor excitability

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ABSTRACT

Purpose: Maintaining joint stability is dependent on the ability of the nervous system to sense and react to potentially injurious loads. In attempts to understand the neurophysiologic mechanisms underlying joint stability, this afferent and efferent activity has been quantified separately at the cortical, segmental and peripheral levels using various electrophysiologic techniques *in vivo*. However, no studies have attempted to quantify sensory and motor activation at multiple levels of the nervous system in a single subset, to understand potential adaptations for optimizing joint stability.

Materials and Methods: Muscle spindle afferent activity and sensory cortex event-related desynchronization were quantified during ankle-joint loading; and motor excitability was assessed through transcranial magnetic stimulation and the Hoffmann reflex in a subset of 42 able-bodied individuals. Microneurography and electroencephalography were used to collect the muscle spindle afferent and sensory cortex activation, respectively, as joint load was applied using an ankle arthrometer. Separately, motor-evoked potentials were obtained from the tibialis anterior (TA) and soleus (SOL) using transcranial magnetic stimulation over the motor cortex, and compared to the reflexive responses evoked via sciatic nerve electrical stimulation.

Results: Correlation coefficients revealed significant correlations between the motor threshold of the soleus and early muscle spindle afferent activity ($r = -0.494$) and early cortical event-related desynchronization ($r = 0.470$), as well as tibialis anterior motor-evoked potential size and late muscle spindle afferent activity ($r = 0.499$).

Conclusions: The results of this study highlight the nervous system's capability to offset motor output based on the volume of sensory input at the segmental and cortical levels.

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Sensorimotor integration; joint stability; neuromuscular control

Introduction

Joint stability is a necessary aspect of daily living characterizing the ability of the sensorimotor system to appropriately regulate joint stiffness in response to anticipated and unanticipated joint loading [1]. One's ability to regulate joint stability about the lower extremity joints is crucial in the avoidance of falls and unintentional lower extremity injury [1,2]. These sensorimotor loops represent a complex physiologic process by which afferent information must pass through peripheral mechanoreceptors, ascend spinal tracts to the somatosensory cortex and develop a muscular response that integrates the efferent output from the motor cortex and spinal reflexes that will serve to stabilize the joint [1]. This process is extremely important about the ankle-joint, given known correlates between ankle stability, ability to maintain postural control and subsequent fall risk. While prior research has utilized *in vivo* techniques to quantify specific levels of this complex response as it relates to joint stability throughout the lower extremity [3–6], no studies have combined these measures in a single subset to determine how scaling of afferent and efferent activity from the peripheral and central nervous systems serve to optimize an individual's joint stability. This information has the potential to aid clinicians and research in the development of interventions better targeted for optimizing joint stability.

Many previous investigations into joint stability have quantified a system's output (muscle activity) in response to a sensory stimulus (joint movement) [7,8]. However, multiple techniques exist for quantifying the peripheral and central levels of the sensorimotor

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response *in vivo*, providing instantaneous and direct neurological correlates of joint loading as it pertains to joint stability [1]. For instance, peripheral afferent activity has been quantified using direct recordings of nerve activity to measure the magnitude of muscle spindle afferent (MSA) responses to joint movement and ligamentous loading using microneurography [9]. The activities from Type Ia and II afferent neurons are readily accessible, and have been utilized to represent a 'final common input' of afferent activity to the nervous system secondary to their ability to adjust sensitivity relative to surrounding mechanoreceptor activity [10]. While this peripheral afferent response may contribute to a segmental motor response, the afferent signal may be further quantified at the cortex through electroencephalography (EEG) [6]. This electrophysiologic cortical activity provides a temporal resolution that is unmatched in other central nervous system imaging techniques, and can therefore provide an indicator of the magnitude of sensory information at the cortical level *throughout* the loading of a joint [11,12]. By combining the microneurography recordings of MSA activity and the EEG recordings of somatosensory cortex activity, we can determine the degree and timing by which joint loading propagates an afferent response in the nervous system.

The motor response for joint stabilization has frequently been quantified through electromyographic (EMG) recordings of muscle activity; however, this is representative of a global response rather than specific cortical and segmental contributions to motor activity [13]. To better discriminate these contributions, technologies have allowed for the measurement of muscle responses from direct stimuli to the cortex via transcranial magnetic stimulation (TMS) [14], as well as the reflexive responses measured from peripheral nerve stimulation termed the Hoffmann reflex (H-reflex) [15]. The amplitude and scaling of these responses combine to provide an understanding of cortical and segmental abilities to generating motor output.

Changes in individual aspects of the nervous system have been identified after ligamentous injury; however, no studies have comparatively assessed the afferent response of joint loading to the corticomotor and reflexive excitability of an individual [16]. Prior research has established relationships between motor excitability and mechanical joint stability (i.e. joint laxity) that potentially indicate increased dynamic protection for the lax joint. Furthermore, this relationship was affected in patients experiencing chronic joint instability [8]. Similar protective relationships may exist whereby patients with a decreased proprioceptive sense of joint loads have enhanced neural excitability in order to appropriately stress-shield the joint, with these potential relationships crucial for understanding joint stability and improving etiological and rehabilitative models of joint injury. We therefore aimed to simultaneously quantify the afferent response of muscle spindles and somatosensory cortex activation in response to ankle-joint loading, and compare these responses to the corticomotor and reflexive output to the tibialis anterior (TA) and soleus (SOL) musculatures. We hypothesized that individuals would display an inverse relationship between the sensory response to joint loading and the motor excitability, with these relationships increasing based on the degree of joint loading.

Materials and methods

Design

This study implemented a correlational design. Dependent variables included MSA amplitude and upper alpha event-related desynchronization (ERD) near the somatosensory cortex in response to joint loading, and active motor threshold (AMT), maximum motor-evoked potential (MEP) size and H-reflex. Participants reported for 2 days of testing, one of which consisted of sensory testing (microneurography and EEG testing), while the other consisted of motor testing (TMS and H-reflex). The order of testing was randomized across subjects with 3–7 days allowed between each day of testing. This period was to allow the subject to recover from the mildly invasive microneurography procedure, while still attempting to test the subjects under similar conditions.

Participants

Forty-two able-bodied individuals (21.4 $\pm$ 3.0 yrs; 169.9 $\pm$ 12.2 cm; 63.8 $\pm$ 12.4 kg) were recruited for this study. All participants were free from injury for at least 1 yr and had no history of fracture or surgery to the lower extremities. The participants were free of any exclusion criteria for the safe practice of TMS, including the presence of metal in the body, history of migraine or seizure disorders, history of heart or brain surgery, medical treatment for psychological disorders or history of neurological disorders [17]. All participants provided university-approved informed consent.

Procedures

Sensory testing

Upon reporting for sensory testing, the participants were fitted with a QuickCap^{TM} (Compumedics Neuroscan, Charlotte, NC), consisting of 32 Ag/AgCl electrodes arranged in accordance with the international 10:20

system. (FP1, FP2, Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, CPz, CP3, CP4, TP7, TP8, Pz, P3, P4, T5, T6, Oz, O1, O2, A1, A2). A ground electrode was placed at the mid-forehead, while linked mastoid processes served as an averaged reference [(A1 + A2)/2] [18]. The conducting medium was added as needed such that the measured impedance was less than 5 kΩ across all channels.

The participants laid on a padded table with the knee flexed at 30°, and an instrumented ankle arthrometer (Blue Bay Research, Milton, FL) was affixed to the ankle and suspended to support the weight of the participant's ankle. A wand-like electrical stimulator (S48 Stimulator, Grass Technologies, Warwick, RI) was used near the fibular head to identify the location of the common peroneal nerve. A tungsten recording electrode was placed at this location while a reference was placed in the nearby skin [19]. The recording electrode was mildly adjusted until the MSA activity was identified by observing the response to slow muscle stretch, silence during shortening and silence during cutaneous stimulation [20]. Electrodes were connected to a Nerve Traffic Analyser (University of Iowa Bioengineering, Iowa City, IA), and signals were continuously displayed on a screen in real-time.

Once EEG and MSA signals were identified, the arthrometer was removed from suspension and 10 anteroposterior translations from a force of −30–130 N (50 N/s) were applied to the ankle, with 5 s rest between trials. While joint loading the ankle is often done using anteroposterior translations or inversion–eversion rotation, we selected to only perform anteroposterior translations as it provided better stability of the recording electrode throughout the trials, and largely loads ligamentous structures as opposed to musculotendinous structures [3]. After each 10-trial block, the presence of MSA activity was reconfirmed, and – if no longer present – the electrode was adjusted until activity was observed. A total of five testing blocks (50 translations) were performed. The participants were asked to keep their eyes open and blink comfortably throughout the testing blocks, while sight of the ankle was obscured with a curtain. Data were collected at 1000 Hz.

Motor testing

For motor testing, the subjects were seated as the areas over the tibialis anterior and soleus muscles were palpated, shaved, cleaned and abraded. Active EMG electrodes were placed at these locations in-line with standard procedures and connected to an amplifier (B&L Electronics, Santa Ana, CA) [21]. The order of cortical or reflexive testing was randomized with a coin flip.

Corticomotor excitability was assessed using single-pulse TMS with a batwing coil (Magstim Ltd, Wales, UK). The participants were seated comfortably in an arm chair with an elastic cap as they were familiarized with the TMS procedures. The hotspot to target the lower extremity muscles was identified using the vertex of the skull and searching a 2 cm radius anterior and lateral to this pulse, while observing the EMG responses in custom software. Once the hotspot was identified, approximately 50 pulses ranging from below the motor threshold to above a maximal response were applied, such that a stimulus–response curve may be formulated. Throughout the delivery of these pulses, the subjects were instructed to pronate their ankle at 15 percent of maximal effort, using real-time biofeedback [22]. The mutiplanar motion of pronation was selected such that drive would be increased without specific activation of the target tibialis anterior or soleus.

Reflexive excitability was assessed using peripheral electrical stimulation with the participant laying prone to allow access to the popliteal fossa. A dispersive electrode was placed over the proximal anterior tibia and a stimulator wand was connected to an electrical stimulator (UD-EL, Newark, DE) and placed in the popliteal fossa. The sciatic nerve was identified in the proximal lateral popliteal fossa prior to its bifurcation by observing a muscle response across all muscles at low stimulation intensity [23]. At this location, 1 ms square pulses were applied, increasing at 2 V increments until no further increase in muscle response was observed. EMG responses were collected at 2000 Hz.

Data reduction and analysis

For sensory testing, physiologic signals of cortical activation were band-pass filtered (0.5–30 Hz) and visually inspected for artifacts. Linear derivation was used to remove ocular artifacts from blinking using electrodes above and below the eye. Trials were partitioned from the start to the end of each joint load and subsequently cut into 4-s epochs consisting of 2000 ms prior to and following the start of each load. The ERD in the upper alpha frequency (10–12 Hz) was calculated from artifact-free segments for the CP3 and CP4 electrodes to correspond with the ipsilateral and contralateral somatosensory cortices (S1). Upper alpha ERD was selected as it has previously been described as a correlate to ankle-joint loading secondary to the suppression of thalamocortical pacemaker cells as afferent information ascends [12]. To quantify the impact of increasing load, the ERD was calculated for the early (0–1000 ms) and late (1000–2000 ms) portions of each joint force application [11,12]. Ensemble MSA activity was amplified (80,000x), filtered (0.7–2 kHz), full-wave rectified and integrated (k = 0.1 s) in the hardware. Trials were reviewed to ensure consistent force application, presence of MSA activity and

Table 1. Means ± standard deviations for measures of joint sensation and motor excitability, including the number of participants from which recordings were obtained.

Joint sensation variables	*N*	Early	Late
MSA activity (% Max)	26	0.127 ± 0.08	0.404 ± 0.16
Alpha-2 ERD (% Max)	30	20.76 ± 22.7	28.35 ± 15.7
Motor excitability variables	***N***	**Tibialis Anterior**	**Soleus**
AMT (%2T)	34	39.97 ± 15.0	37.22 ± 14.8
MEP max (ratio of M_{max})	34	0.389 ± 0.28	0.079 ± 0.07
H:M ratio (ratio of M_{max})	37	0.178 ± 0.12	0.458 ± 0.25

absence of extraneous noise. Afferent activity was normalized to the peak voltage of each trial block and assessed through the early (0–1000 ms) and late (1000–2000 ms) portions of joint loading.

Corticomotor excitability was determined by evaluating the peak-to-peak MEP amplitudes from each muscle, and plotting these against stimulus intensities to form a stimulus–response curve. Amplitudes were normalized to the maximal response from peripheral nerve stimulation (M_{max}). Stimulus–response curves were fitted with a modified Boltzmann equation using the Levenberg–Marquardt algorithm ($R^2 \geq 0.75$) to extract the maximum MEP response and derive the AMT as the intensity at which the slope of the curve increased to 10 per cent of its peak [24,25]. For reflexive excitability, the EMG data were analysed for peak-to-peak amplitude from 10–40 ms following the stimulus; and 50–100 ms following the stimulus. These windows represent the motor response (M-wave) and reflexive response (H-wave), respectively [15]. The maximum H-wave was divided by the maximum M-wave and this H:M ratio was extracted for analysis.

Relationships between sensory variables (ERD and MSA activity) during early and late joint loading were compared to the measures of corticomotor and reflexive excitability (MEP_{max}, AMT, H:M ratio) using Pearson product–moment correlation coefficients. Five subjects did not report for a second testing session, and therefore were not used for analysis. Additionally, variable-specific data were considered missing and not included for analysis if: (1) an insufficient number of artefact-free EEG segments during joint loading (≤25) were obtained to calculate ERD; (2) MSA signal was not identified within time parameters to limit the chance of residual symptoms in the area [26]; or (3) MEP data were unable to be fitted to a stimulus–response curve with good fit ($R^2 \geq 0.75$). The exact number of subjects completing each measure is included in Table 1. An a-priori level of significance was set at 0.05.

Results

The mean values of dependent variables are presented in Table 1. As expected, the sensory responses at the muscle spindle and sensory cortex ERD were observed to increase as load was applied (early compared to late periods). Statistically significant correlations were observed between soleus AMT and early MSA ($r = -0.494$, df = 18, $P = 0.027$), as well as early sensory cortex ERD ($r = 0.470$, df = 20, $P = 0.027$) (Table 2, Figure 1). A trend was observed correlating soleus AMT with late MSA activity ($r = -0.439$, df = 18, $P = 0.052$). Late MSA activity was observed to correlate with tibialis anterior MEP_{max} ($r = 0.499$, df = 20, $P = 0.018$).

Discussion

The current study aimed to determine how the sensory response to joint load correlated with motor excitability of the nervous system at peripheral and cortical levels. The primary findings of this study indicated that higher ensemble MSA activation in response to joint loading is associated with greater corticospinal excitability to the soleus and tibialis anterior. Although contrary to our hypothesis, this finding suggests that the motor cortex may increase excitability proportionately to the amount of peripheral sensory activity it receives. Given previously described alterations in MSA sensitivity and motor excitability among subsets of patients with chronic joint injury, these findings have important implications for the neural mechanisms contributing to joint stability and subsequent injury prevention.

MSA activity was consistently observed to associate with corticomotor excitability to the ankle musculature, although differently among the phasic tibialis anterior and postural soleus muscles. For the soleus, this relationship was related to the motor threshold, believed to quantify the membrane polarity of cortical neurons and subsequent 'ease of contraction'. Alternately, the tibialis anterior

Table 2. Pearson product–moment correlation coefficient values (*r*) for relationships between measures of sensory function (rows) and motor excitability (columns). *Significant at $P < 0.05$.

		AMT		MEP_{max}		H:M ratio	
		Tibialis Anterior	Soleus	Tibialis Anterior	Soleus	Tibialis Anterior	Soleus
MSA activity	Early	−0.072	−0.494*	0.060	−0.217	−0.203	−0.162
	Late	−0.231	−0.439	0.499*	−0.143	0.011	0.106
Sensory cortex ERD	Early	−0.343	0.470*	0.228	0.156	0.009	−0.018
	Late	−0.303	0.338	0.310	0.320	0.087	0.135

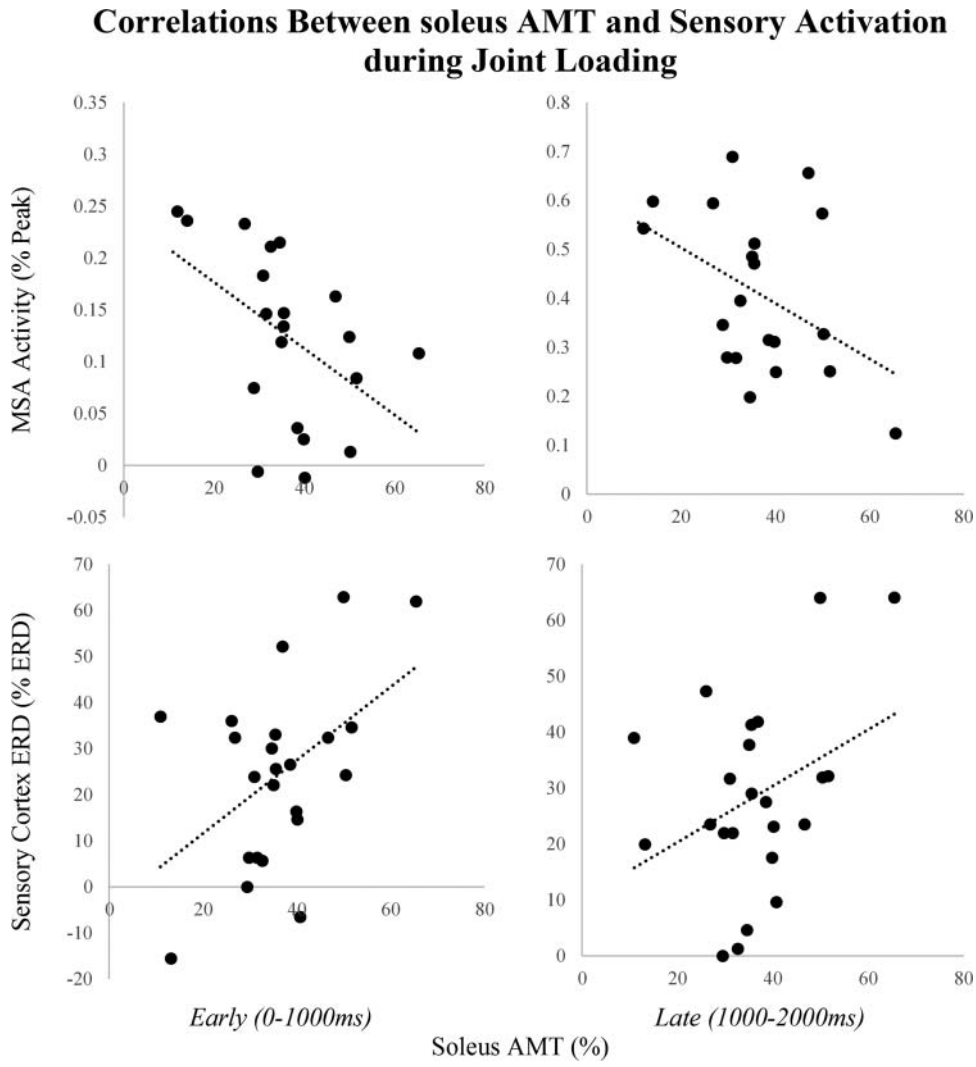

Figure 1. Correlation scatter plots of sensory activity on the vertical axes [top row: muscle spindle afferent (MSA) activity (% Max); bottom row: sensory cortex event-related desynchronization (ERD) (% Max)] with soleus active motor threshold (AMT, %2T) on horizontal axes across time points [left column: early (0–1000 ms from load onset); right column: late (1000–2000 ms from load onset)].

related to MSA through the MEP_{max} that represents neuronal availability for firing [24,27]. No previous studies have quantified the MSA response to load and corticomotor excitability among the same *in vivo* subset. The afferent traffic collected in this study is important for several reasons as the muscle spindle not only has a key role in regulating spinal reflexes and muscle tone, but also serves as a 'final common input' to the central nervous system because of its ability to modify sensitivity segmentally from surrounding mechanoreceptor activity [10,28,29]. It may therefore be concluded that as sensory feedback increases to the nervous system, so should corticomotor excitability. The sizes and threshold of MEPs have previously been identified as being predictive of muscle tone, through studies in impaired populations (i.e. dystonia), or by concurrently measuring joint stiffness [25,30,31]. This relationship exists because of the ability of TMS to activate not only excitatory descending pathways, but also intracortical inhibitory pathways. Increased MSA activity would therefore indicate a higher level of fusimotor gain (α–γ coactivation) that would increase cortical excitability, but also greater input to the cortex that may subsequently raise excitability [32].

Greater cortical excitability to the soleus was observed to increase with MSA activity; however, participants with greater cortical excitability to the soleus displayed less early sensory cortex ERD. As the ankle is loaded, multiple afferent pathways would be activated within the central nervous system. Whereas microneurographic assessment of MSA activity in this context extracts a sensory signal with few influences from central nervous system tracts [19], the desynchronization in the area of the somatosensory cortex represents an ensemble activation arising to the cortex that causes suppression of corticothalamic pacemaker cells [33]. The relationships observed in this study potentially indicate the ability of the cortex to offset changes in MSA activity when regulating corticomotor output, such that the

somatosensory cortex can inhibit MSA activation for individuals with heightened muscle tone [34]. This could subsequently allow for improved regulation of motor recruitment in the preparation and response to joint loads. Previous findings have observed the sensory feedback to affect cortical output in paradigms utilizing nerve blocks [35]; however, this study is the first to demonstrate the ability of the cortex to modify cortical excitability relative to somatosensation across a population. Our findings are consistent with theories suggesting that improved sensation translates to a decreased need for motor recruitment to maintain joint stability, through mediation of the fusimotor system [1,35]. This may explain why proprioception deficits alone have failed to identify individuals at increased risk of injury.

A final notable finding of this study was the lack of correlations observed regarding reflexive excitability. The H-reflex quantifies the size of muscle activation from reflexive pathways mediated by MSA to the direct, well-controlled stimulations of alpha motor neurons [15]. While this measure should be tied to MSA sensitivity, no correlations were observed between any MSA and reflexive excitability measures. This may be explained by some key methodological differences between the microneurographic assessment and H-reflex procedures. First, MSA activation was assessed using a slow, gradual joint load rather than a rapid perturbation that would elicit a reflexive response. While a faster load may highlight a relationship between these measures, it would not be conducive to *in vivo* recordings of MSA activity. Additionally, the H-reflex is most often assessed for the tibial nerve in the lower extremity, as this value is typically greatest in the triceps surae, whereas microneurographic recordings were obtained from MSA within the common peroneal nerve. Perhaps, comparing reflexive excitability of the soleus to tibial nerve MSA activity would highlight potential relationships in segmental sensorimotor control.

Recent investigations into patients with joint instability have described deficits in reflexive excitability, quantified through the H-reflex, considering it predictive for joint injury and instability [4,36]. However, the results of this study suggest that this measure may not fully explain the deficits in these populations. Few studies have quantified cortical excitability after joint injury, and fewer studies have quantified cortical sensory activation [16]. However, it appears that these factors may be more predictive of neurological changes than previously thought and should be included in subsequent neurophysiologic research into joint stability mechanisms.

While this study was the first to combine *in vivo* measures of nervous system activity in a single population, some limitations exist. First and foremost, attrition occurred regarding our sensory measures due to success rates with microneurography recordings (65 per cent) and the ability to obtain a sufficient number of artifact-free EEG segments for ERD analysis. These measures also present limitations, as ERD analysis of electrical cortical activity provides limited spatial resolution. Additionally, while MSA activity was confirmed for each subject, it is possible that additional afferent activity from other receptors may have contributed to the observed signal. Finally, this study quantified four distinct locations of nervous system activity; however, we were unable to control for other influences, notably from the brainstem, vestibular system and cerebellum. Further research may attempt to incorporate these additional locations of testing to better understand the role of these various influences in maintaining joint stability.

Conclusions

This investigation has identified multiple relationships among sensorimotor function that may facilitate the maintenance of joint stability. Previous studies have identified deficits in MSA activity, sensorimotor cortex activation, corticomotor excitability and reflexive excitability across various subsets of unstable joints. However, the relationship between these variables has not been previously described in a single population. Results suggest that corticomotor excitability to the tibialis anterior and soleus muscles is directly scaled to the sensitivity of muscle spindles, and that sensory activation is inversely scaled to the corticomotor excitability of the soleus. These findings highlight the advanced ability of the nervous system to adapt the motor output scaled for sensory activation present in an individual. When considering improving nervous system function, interventions for improving corticomotor output may be beneficial for improving MSA activity, and vice versa. Our findings may be further analysed with respect to functional measures of joint stability, such as balance and muscular activation during walking and athletic manoeuvres, and incorporating these measures among different populations such as those with joint injury.

Disclosure statement

No potential conflict of interest was reported by the authors.

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