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RESEARCH ARTICLE | *Control of Movement*

Cross-limb dynamics of postural tremor due to limb loading to fatigue: neural overflow but not coupling

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Morrison S, Kavanagh JJ, Newell KM. Cross-limb dynamics of postural tremor due to limb loading to fatigue: neural overflow but not coupling. *J Neurophysiol* 122: 572–584, 2019. First published May 8, 2019; doi:10.1152/jn.00199.2019.—Many experiments have shown independence of the index finger dynamics under bilateral postural tremor protocols. Here we investigated in young adults the dynamics of bilateral multidirectional postural tremor and forearm muscle activity under the progressively fatiguing conditions supporting an external weight to the point of induced postural failure. When no loads were applied, tremor in the vertical (VT) and mediolateral (ML) directions was similar with prominent peaks within 2- to 4-Hz and 8- to 12-Hz bandwidths. Contrastingly tremor in the anterior-posterior (AP) direction was characterized by a single peak between 0 and 2 Hz. Although no tremor coupling occurred cross limbs, strong within-limb coupling was found between ML and VT directions when no loads were applied (coherence range: 0.77–0.85), implying that these oscillations are related and likely derived from mechanical sources. Applying an external load to the index finger(s) led to significant increases in the amplitude of VT tremor and EMG activity within that limb but also caused increases in tremor directions not aligned with the gravitational vector (AP and ML). Significant increases in VT and ML tremor and EMG activity in the contralateral (unloaded) limb were also found when a single index finger was loaded; however, this bilateral increase did not align with increases in interlimb coupling (coherence <0.21). The effects of fatigue caused by prolonged loading were widespread, affecting tremor and muscle activity in both limbs through a combination of neural and mechanical mechanisms. The single- and dual-limb loading to fatigue increased neural overflow but not tremor coupling between the index fingers.

NEW & NOTEWORTHY This study investigated bilateral multidirectional tremor under unloaded and loaded conditions. We found that tremor in the mediolateral and vertical directions within a limb were strongly coupled, a result not reported previously. Furthermore, when holding a weight to failure, tremor in all directions increased. Tremor also increased in the contralateral (unloaded) limb despite no interlimb coupling. This contralateral increase in tremor following loading a limb until fatigue is hypothesized to stem from motor-overflow effects.

bilateral; coupling; fatigue; loading; tremor

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INTRODUCTION

The small fluctuations or oscillations observed in a limb held against gravity are commonly referred to as postural tremor (Elble 1996; Elble and Koller 1990). These fluctuations reflect the aggregated output from a variety of sources including the mechanical resonant properties of the limb it is observed from, cardiac mechanics, central neural mechanisms, and peripheral contributions related to stretch reflexes (Elble 1996; McAuley et al. 1997; Stiles and Pozos 1976; Stiles and Randall 1967). Despite similarity in the mechanisms underlying the generation of tremor, the oscillations seen within a single limb are uncorrelated to those in the contralateral limb (Marsden et al. 1969; Morrison and Newell 1996, 1999). The assumption underlying the independence of bilateral relations has been that the limb tremor in each arm is driven by parallel oscillators within the central nervous system (CNS; Ben-Pazi et al. 2001; Köster et al. 1998; Llinas 1984; Marsden et al. 1969) and that coupling will only emerge with the development of certain neurological diseases such as essential tremor and orthostatic tremor (Chakraborty et al. 2017; Poon et al. 2011; Raethjen et al. 2000).

Despite the lack of tremor coupling between limbs, several studies have documented interventions that not only increase tremor amplitude in one limb but also produce a parallel increase in tremor amplitude for the contralateral limb. For example, voluntary cocontracting the muscles of a single limb (Daneault et al. 2010; Morrison and Newell 2000), increasing the force requirement through the application of external loads to one limb (Kavanagh et al. 2013), and exercising a single limb to fatigue (Boonstra et al. 2008; Morrison et al. 2005; Morrison and Sosnoff 2010) have all been shown to increase tremulous and/or EMG activity in the contralateral limb. This effect has been interpreted to reflect, in part, the overflow of neural activity to the muscles of the contralateral limb (Zijdewind et al. 1998; Zijdewind and Kernell 2001). In this view, the basis for these bilateral changes is driven by central neural mechanisms rather than through peripheral inputs (neural or otherwise) so that increased activation within the higher levels of the CNS incidentally produces motor activity in pathways that project to muscles of the nonactive limb. The combination of increased descending neural drive coupled increases in the gain of motor neuron activity (driven by simultaneous increases in neurotransmitters such as serotonin; Heckman et al.

2009) may subsequently lead to increases in muscle activity in the contralateral (i.e., nonactive) limb.

While much of the interest in the phenomena is related to the benefits for exercise and training (Bodwell et al. 2003; Green and Gabriel 2018; Hortobágyi et al. 1997, 1999; Ruddy et al. 2017), there has been a growing interest in the mechanisms that underlie this bilateral response. For example, while the contralateral increases in tremor and muscle activity are commonly seen with activity in a single limb, this type of activity does not lead to increased coupling between the limbs, which tend to remain unaffected (Morrison et al. 2005; Morrison and Newell 1996). It would appear as if independence of the intrinsic oscillations between limbs is the prevailing pattern for bilateral tremor in many healthy adults, both young and old. Furthermore, disorders that affect the CNS (such as Parkinson's disease) and even physical amplified tremor do not increase the level of coupling between the segments of the arms (Morrison et al. 2008a, 2008b). Functionally, the perseverance of independence between the limbs under postural conditions may afford the neuromotor system greater flexibility for voluntary movements. Having a state where the contralateral limbs are effectively uncoupled could facilitate independent movements of each arm more so than if the limbs were linked to some degree.

It is possible that the strength of any interlimb coupling is driven (in part) by increased activation of task-specific muscles. Indeed, previous research has described how coupling between the same effectors changes as a function of the specific bilateral task being performed (Morrison et al. 2012). In this study, the level of coupling between the index fingers increased systematically from a postural tremor task to an isometric task to an isotonic movement. A feature of the reported changes in coupling from the tremor tasks was the increased force requirement for the (bilateral) isometric and isotonic activities. Contrastingly, simply stiffening (cocontracting) the muscles of one or both arms has been reported to not affect bilateral coupling of tremor (Morrison and Newell 2000) although specific measures of EMG were not performed in this study. It has also been reported that bilateral coupling of tremor is not increased following exercise-induced fatigue (Morrison et al. 2005), but the coupling assessments of this study were performed following the fatigue intervention (i.e., postexercise) and not during the actual task itself. Thus directly assessing bilateral coupling during the performance of the fatiguing task may reveal more about the potential of bilateral tremor relations. Furthermore, combining load and fatigue protocols whereby individuals are required to hold an external weight to the point of failure may stress the system to a point where bilateral coupling emerges. Such a task would incorporate near-maximal muscle force production under fatigue-type conditions.

The coupling of tremor may be differentially evident in each of the planes of motion of tremor within a limb. When holding a limb against gravity and measuring tremor, the underlying assumption is that control over vertical (VT) motion is the greatest challenge. However, tremulous motion is not limited to a single plane of motion and can be seen in the mediolateral (ML) and anterior-posterior (AP) directions (Hong et al. 2008; Kelleran et al. 2016; Lakie et al. 1995; Tang et al. 2008). Indeed, several studies have reported that oscillations in the ML direction are comparable in amplitude to that seen in the VT direction (Kelleran et al. 2016; Pellegrini et al. 2004; Tang et al. 2008) although the exact origin(s) of the ML tremor component still needs to be determined. Similarly, there have been very few studies that have captured postural tremor in the AP direction for comparison. Of the few studies that have incorporated assessments of tremor in the AP direction, Tang and colleagues (2008) and Kelleran et al. (2016) both reported that AP oscillations were lower in magnitude compared with the VT and ML tremor during a pistol shooting task. Speculation as to the potential origin for AP tremor has included postural sway and cardiovascular and/or respiratory events although not definitive answer has been reported to date. This is relevant to the potential bilateral coupling because the tremor in the ML and/or AP plane is less affected by gravity during assessments of finger position. However, given that most muscles tend to produce motion in more than one direction, there exists the possibility that enhanced mechanical and/or neural overflow would influence cross-limb coupling between ML, AP, and VT oscillations despite the lack of any gravity effect.

The current study was designed to investigate the influence of single- and dual-limb loading with and without fatigue on bilateral index finger tremor and forearm muscle activity. For this assessment, changes in the tremor profile for each index finger in the AP, ML, and VT directions were examined in the time and frequency domains. Data analyses were structured around the following questions, namely, *1*) what are the characteristics of multidirectional index finger tremor for both arms under unloaded (control) conditions; *2*) how does holding an external load to postural failure affect index finger tremor (in the VT, AP, and ML directions), forearm muscle activity in the unloaded contralateral limb, together with their bilateral coupling relations; and *3*) what impact does fatigue have on the time course of finger tremor? It was predicted that, under unloaded (control) conditions, while tremor would be more evident in the VT direction compared with the AP and ML fluctuations, strong coupling between ML and VT tremor would be found. Furthermore, performance of a prolonged loading task, where individuals are asked to hold an external weight until fatigue-induced failure, would lead to a bilateral increase in tremor and muscle activity but no changes in the strength of interlimb coupling of tremor. Finally, tremor would show a systematic change in both amplitude and structure over the time course of the loading conditions due to the effect of fatigue.

METHODS

Participants

Eighteen adults (10 males, mean age: 23.5 ± 0.9 yr, height: 184.2 ± 11.2 cm, weight: 88.3 ± 16.2 kg; 8 females, mean age: 25.1 ± 0.7 yr, height: 173.4 ± 7.5 cm, weight: 82.3 ± 13.6 kg) participated in this study. All participants were recreationally active and reported no neurological disorders or neuromuscular injury that could influence performance. Twelve hours before testing, participants were required to abstain from any form of stimulant that may impact on limb tremor (e.g., alcohol, caffeine) or moderate-high intensity exercise. All participants provided written informed consent before testing. All experimental procedures and protocols were submitted to and approved by the Institutional Review Board (IRB) for Old Dominion University.

Experimental Design

Individuals participated in a series of experiments where physiological tremor was assessed during single-limb and dual-limb loading. Index finger acceleration (tremor) and surface electromyographic (EMG) activity for the extensor digitorum (ED) and flexor digitorum (FD) of both limbs were collected for all conditions. Tremor was recorded using two light weight (2.8 g) Noraxon triaxial accelerometers (Noraxon, Scottsdale, AZ). These devices were attached to the dorsal, distal aspect of each index finger. EMG activity was recorded using paired Ag/AgCl surface electrodes that were positioned over the belly of the ED and FD muscles of both upper limbs. Electrodes were placed with an interelectrode distance of 2 cm and in parallel with the direction of the underlying muscle fibers. Preparation of the skin for the surface electrodes involved shaving the skin and then cleaning with alcohol wipes. All accelerometer and EMG data were collected using a 16 channel Noraxon Telemyo system (Noraxon) with a sample rate of 1,500 Hz. For the purposes of this study, the hand individuals used to write with was designated as their preferred arm and the opposite arm the nonpreferred.

Assessment of Resting Muscle Activity

Baseline (resting) muscle activity was collected before the loading protocol. The subject's forearm, hand, and fingers of both arms were positioned on a flat surface, fully supported. Three 30-s trials were performed with EMG data collected from all selected muscles.

Determination of Weights for Limb Loading

Determination of the designated loads for each person was calculated by attaching a weight to a single index finger and having each person hold this load against gravity for more than 30 s without any obvious tremor or discomfort. The weight range across all persons was 50 to 100 g. For each person, the same weight was used for all unilateral and bilateral conditions. A 5 min rest was permitted at the completion of this task.

Assessment of Maximal Voluntary Contraction

Following the resting (baseline) levels and loading determination, maximal voluntary contraction (MVC) was determined for wrist extension and wrist flexion. This assessment was performed since EMG activity was recorded from the ED and flexor FD muscles. MVCs were performed for each arm individually. For each MVC, participants performed three maximal isometric contractions of 5-s duration against a fixed load, where a rest period of (up to) 5 min was provided between each contraction. The greatest MVC for the three trials was taken to represent each subject's MVC. The difference in amplitude between the baseline (resting) activity and MVC contraction was used as the value for MVC determination. A 10-min rest was permitted at the completion of the MVC task.

Loading Protocol

Participants were seated comfortably with the elbow flexed at 90° and forearms resting on a flat surface. The hand was held unsupported with individuals adopting a pointing posture using their index fingers only. In this position, the index finger extended at the metacarpophalangeal joint, the thumb adducted, and the remaining fingers flexed to form a loose fist (Fig. 1). All participants were instructed to focus on the end of their index fingers to minimize the motion (i.e., tremor) at that point. Individuals were not permitted to change the position of the remaining fingers or thumb during the course of the study. For each condition, care was taken to ensure the persons held their hand/finger in the same position and they were instructed not to lift their forearm off the flat support surface nor were they permitted to rotate their hand/finger (i.e., through forearm supination or pronation) or flex/extend their wrist during any of the tasks.

Participants performed two trials for each condition, with 1–2 min of rest between each trial. The conditions performed were as follows: first, no weighting: participants held both index fingers against gravity as described above. This condition was used as the control condition for comparison to the unilateral and bilateral weighting (i.e., fatigue) conditions. Two 2-min trials were performed for this condition. Second, unilateral weighting: participants held both index fingers against gravity and a light weight was added to the index finger of one limb. Participants were asked to hold both index fingers steady for as long as possible against gravity with the weight attached. After the completion this task, a rest period of 1–2 min was provided, and the weight was applied to the opposite limb. Third, bilateral weighting: participants held both index fingers against gravity and a lightweight was added both index fingers. Participants were asked to hold both fingers steady against gravity for as long as possible with the weight

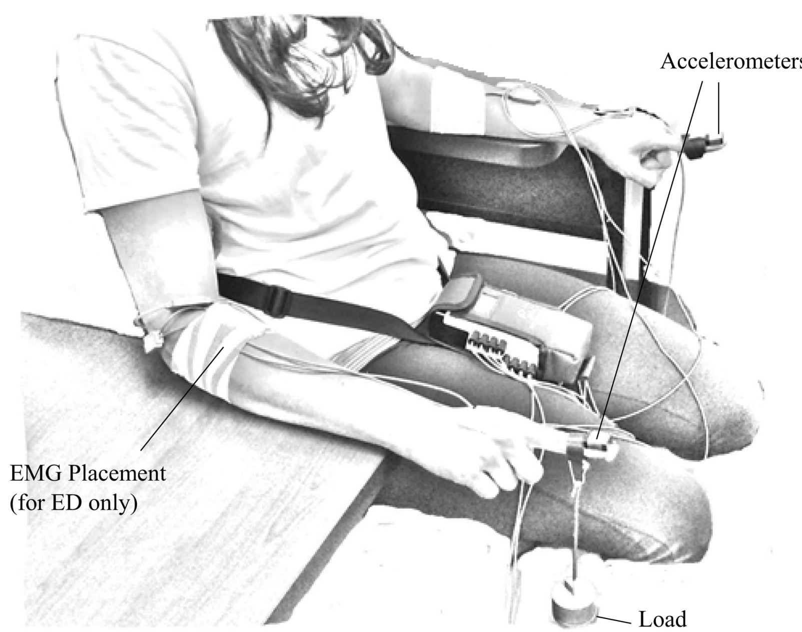

Fig. 1. Graphical illustration of the experimental setup during loading of both index fingers. Positions of the accelerometers and surface electrode placement are shown. ED, extensor digitorum.

attached. For all loading conditions, there was no set trial length as responses were collected until the subject could no longer hold the weight against gravity. Task failure was defined as the point where the individuals could no longer maintain the horizontal finger position while holding the weight. Generally, if the individual dropped their finger by >15° (~1.5 cm) for >3 s, the trial was halted. At the point where individuals dropped their finger(s), data collection was halted and the weight was quickly removed. Figure 1 provides a general illustration of the position of the participant and setup for the unilateral weighting condition.

Data Analysis

Before analysis, the acceleration data were downsampled to 100 Hz, rectified, and filtered using a second-order low-pass Butterworth filter (cut-off frequency: 40 Hz). The EMG data were rectified and filtered using a second-order low-pass Butterworth filter (cut-off frequency: 400 Hz). All filtering and rectification were performed offline after data collection was completed. All data analyses were performed using custom software developed in MATLAB (MathWorks R14).

Tremor Amplitude

Both time and frequency domain analyses were performed to assess changes in tremor amplitude. The time domain analysis involved calculating the root mean square (RMS) of the tremor signal in each of the three directions (i.e., AP, ML, and VT). Frequency analyses were performed using Welch's averaged, modified periodogram method (window: 512 data points; bin size: 0.1953 Hz) within three specific frequency bins (0–7, 7–17, and 17–30 Hz) as per previous research (Morrison et al. 2005; Morrison and Newell 1996). The maximum amplitude of each signal (peak power) within each bin was calculated.

Tremor Regularity

The degree of regularity of the acceleration signals was assessed using Sample Entropy (SampEn; Richman and Moorman 2000). This analysis measures the time-dependent repeatability of the acceleration signal, producing a single value within the range of 0–2. Typically, signals with higher values indicate increased irregularity/complexity, while lower values (closer to 0) representing greater regularity or structure in the signal.

EMG Amplitude

An estimation of the average amplitude of muscle activity was determined by calculating the RMS of the EMG signal for each muscle. The average of the full-wave rectified EMG signal was used to assess the degree of muscle activation.

Coupling Analysis

Coherence analysis was performed to provide an estimate of the degree of directional coupling within limb (i.e., for the index finger tremor across each direction AP-ML, ML-VT, and AP-VT) and between arms (i.e., between index finger-finger in the same direction only, i.e., AP-AP, ML-ML, and VT-VT). This analysis is a normalized linear measure of coupling whereby significant levels of coherence can be used to estimate coupling between two signals in the frequency domain. The equation for coherence (Cxy) is as follows:

$$Cxy = \frac{\left[abs\left(Pxy\right)2\right]}{\left(Pxx \times Pyy\right)}$$

where Pxx and Pyy are the power spectral density estimates of signal x and y, respectively, and Pxy is the cross-power spectral density estimate of signals x and y. For this analysis, the amplitude and frequency at which significant coherence was observed are reported with higher coherence values (i.e., closer to 1) indicate increased coupling between the two signals. This analysis was performed within the range 0–30 Hz as per previous tremor research (Morrison and Newell 1996; Vaillancourt and Newell 2000). To determine whether the level of coherence between any two signals was significantly different from zero, a 95% confidence interval (CI) was calculated according to the methods described by Halliday et al. (1995). For this calculation, coherence values lying below the 95% CI value can be taken as evidence that, on average, no coupling occurs between the two signals at that frequency (Amjad et al. 1997).

Statistical Analysis

Statistical analyses were structured to address three questions: *1*) what are the characteristics of multidirectional index finger tremor for both arms under unloaded (control) conditions; *2*) what effect does holding an external load to postural failure have on index finger tremor (in the VT, AP, and ML directions), forearm muscle activity in the unloaded contralateral limb, together with their bilateral coupling relations; and *3*) what impact does fatigue have on the time course of finger tremor?

For *question 1*, a repeated-measures mixed generalized linear model (GLM) was used to assess for differences in the accelerometer and EMG measures under the unloaded (control) condition only. Differences were assessed as a function of direction (i.e., AP, ML, and VT) and limb (preferred and nonpreferred limb). For *question 2*, a repeated-measures mixed GLM was used to assess for differences in the accelerometer and EMG measures as a function of condition (i.e., unweighted, unilateral loading, and bilateral loading) and limb (i.e., preferred and nonpreferred limb). Tremor data were assessed for each direction (AP, ML and VT) separately for this analysis. For *question 3*, a repeated-measures mixed GLM was used to assess changes that occur in tremor amplitude within the initial part (i.e., first 20%) and last part (i.e., last 20%) of the trials within each specific task condition. Tremor data were assessed for each direction (AP, ML, and VT) separately for this analysis. For all analyses in the study, significant interaction effects were explored using planned contrasts (one-way ANOVA) within the mixed model design. All tests were performed using SAS statistical software (SAS Institute, Cary, NC), with the risk of type I error set at $P < 0.05$.

RESULTS

Bilateral Characteristics of Multidirectional Finger Tremor Under Unloaded Conditions

During unloaded conditions, index finger tremor in the VT and ML directions was characterized by prominent frequency peaks between 2 and 4 Hz and between 8 and 12 Hz (see Fig. 2). In contrast, tremor in the AP direction only exhibited a single low amplitude and frequency peak between 0 and 2 Hz. As there were no prominent peaks observed above 17 Hz for tremor in the AP, ML, or VT directions, frequency analysis was restricted to the 0- to 7-Hz and 7- to 17-Hz ranges.

In regards to amplitude, both the RMS and frequency analyses revealed that the tremor was greatest in the VT direction followed by the ML and AP acceleration components (RMS: $F_{2,34} = 250.63$; 2- to 4-Hz peak: $F_{2,34} = 35.19$; 8- to 12-Hz peak: $F_{2,34} = 57.59$; $P < 0.001$). It should be noted that, as tremor in the AP direction exhibited no significant peaks above 5 Hz, analysis of the 8- to 12-Hz frequency peaks was restricted to VT and ML tremor components only. For signal regularity, tremor in the VT direction had the highest SampEn

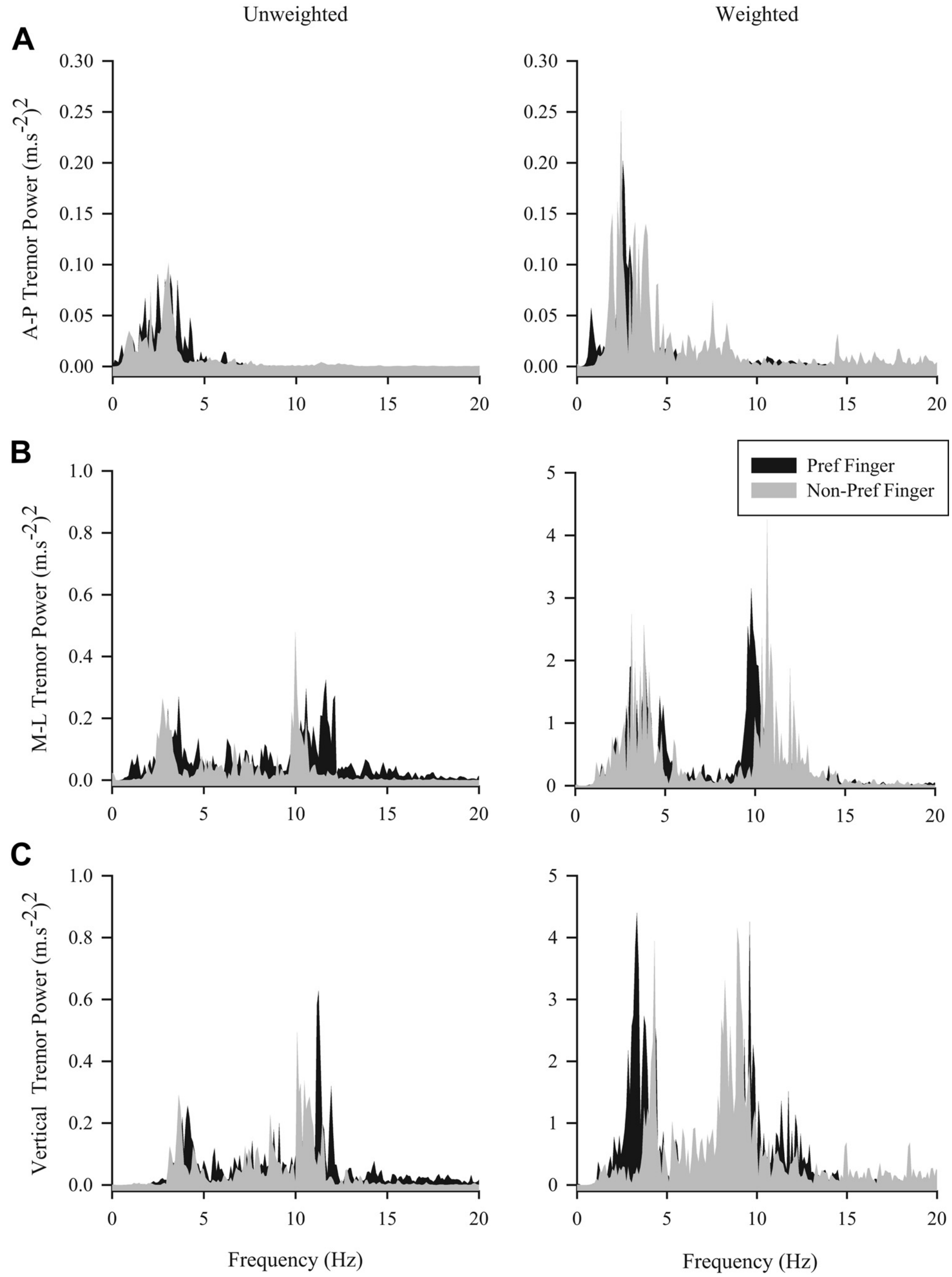

Fig. 2. Representative power spectral plots illustrating differences in the anterior-posterior (A-P; *A*), mediolateral (M-L; *B*), and vertical (VT; *C*) tremor signals for the index finger of each arm. Traces also show the general pattern of change with weighting (*right*) compared with the unweighted (*left*) conditions. Pref, preferred; Non-Pref, nonpreferred.

value followed by the ML and AP acceleration components ($F_{2,34} = 76.27$, $P < 0.001$). No limb effects or limb-by-direction interaction effects were observed for the RMS ($P > 0.62$), frequency ($P > 0.43$), or SampEn ($P > 0.13$) analyses.

The results of the coherence analysis for the within-limb comparisons revealed a significantly high level of coupling between the tremor in the VT-ML directions within 2–4 Hz and 8–12 Hz (coherence values: 0.77–0.85, $F_{2,34} = 19.21$; $P < 0.01$). Coupling was also found between the tremor in the AP-VT (coherence 0.44) and AP-ML directions (coherence 0.55) although the only prominent frequency peak for the AP signal was between 0 and 2 Hz. For the level of coupling between limbs during the unloaded task conditions, no significant coupling was found between the index finger tremor in any direction (all coherence values <0.21).

Effect of Loading on Tremor, Muscle Activity, and Bilateral Coupling

For the unilateral loading conditions, the average times to failure were 91.9 ± 12.5 s (loading of preferred limb) and 93.2 ± 12.31 s (loading of the nonpreferred limb). For the bilateral loading condition, the average time to failure was 81.6 ± 10.9 s. One-way ANOVA results indicated that the time taken to fatigue was not significantly different across the various loading conditions ($P = 0.25$).

Multidirectional tremor. The addition of an external weight to the index finger led to a systematic increase in three-dimensional tremor amplitude for both the loaded limb and the unloaded limb. This was evident from the amplitude analyses of RMS acceleration (VT: $F_{3,51} = 57.34$; ML: $F_{3,51} = 66.87$;

AP: $F_{3,51} = 63.18$; $P < 0.001$) and for the frequency results. Specifically, for the frequency analysis, significant increases in power were found for the 2- to 4-Hz (AP: $F_{3,51} = 21.37$; ML: $F_{3,51} = 10.59$; VT: $F_{3,51} = 60.29$; $P < 0.001$) and 8- to 12-Hz peaks (ML: $F_{3,51} = 13.31$; VT: $F_{3,51} = 13.62$; $P < 0.001$; see Fig. 2). Planned contrasts revealed that during conditions where only a single index finger was loaded, a significant increase in tremor in the unweighted limb (from the control condition) was also observed ($P < 0.01$). Furthermore, the only conditions where there was no difference in tremor amplitude (either RMS or frequency) was between the unilateral loading (weighted limb only) and bilateral loading conditions ($P > 0.42$). No main effects for limb or interaction (limb-by-condition) effects were observed. Figure 3 illustrates the bilateral differences in RMS acceleration in the VT and ML directions across conditions.

The effect of adding an external weight was also reflected by changes in tremor regularity (ML and VT only) that systematically decreased with loading (VT: $F_{3,51} = 124.66$; ML: $F_{3,51} = 11.03$; $P < 0.001$). As with the amplitude results, during conditions where only a single index finger was loaded, a significant increase in tremor regularity (i.e., decreased SampEn) from con-

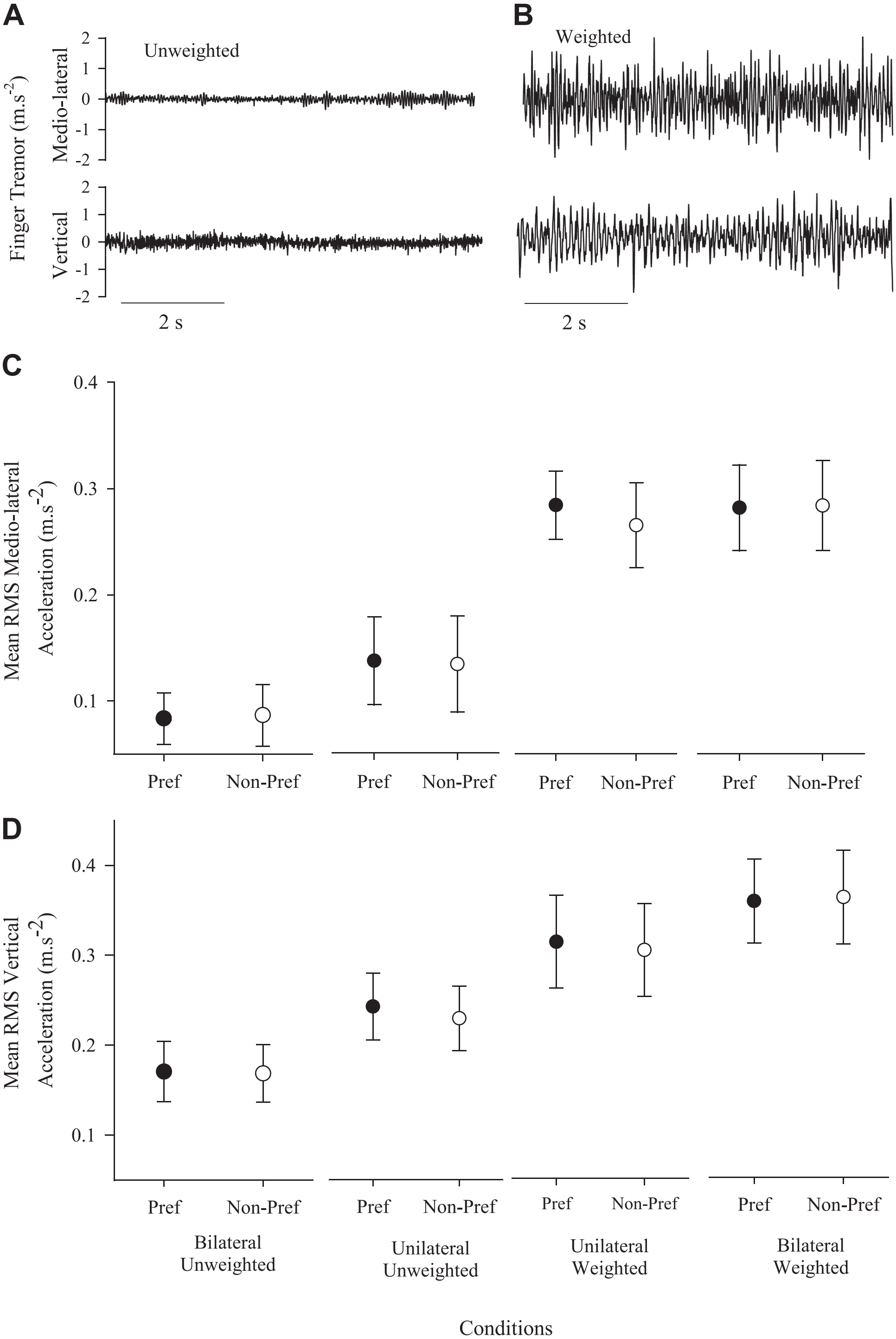

Fig. 3. Representative signals for the tremor in the vertical and mediolateral directions during the unweighted (*A*) and weighted tasks (*B*) for a single subject. Tremor data were attained for the preferred index finger during a single trial. Plots illustrating average changes in the vertical (*D*) and mediolateral (*C*) index finger tremor [mean root mean square (RMS)] across the different task conditions (i.e., bilateral unweighted, unilateral weighted and bilateral weighted) are also shown. For *C* and *D*, values are shown for both the preferred (Pref) and nonpreferred (Non-Pref) limbs for each condition. Error bars represent means ± 1 SD.

trol condition values was still observed. The SampEn values for tremor in the ML and VT direction across the four conditions are shown in Fig. 4. No changes in SampEn values for AP tremor were observed with loading (all $P < 0.05$).

Muscle activity. Adding an external weight (either unilaterally or bilaterally) led to a systematic increase in muscle activity for both the forearm extensors ($F_{3,51} = 41.50$; $P < 0.001$) and flexors ($F_{3,51} = 31.06$; $P < 0.001$). Consistent with the tremor amplitude analyses, during conditions where a single index finger was loaded, a significant increase in both the flexor and extensor muscle activity in the contralateral, unweighted limb (from the control condition) was also observed (all $P < 0.02$). Furthermore, the only conditions where there was no difference in EMG amplitude was when a single limb or both limbs were loaded (all $P > 0.11$). Figure 5 illustrates the difference in RMS amplitude for the extensor and flexor muscles across the various unweighted/weighted conditions.

Coherence analysis. Figure 6 illustrates both the pattern of within-limb and between-limb coherence coupling values for each of the task conditions. The addition of the external weights resulted in an increase in the strength of all within-limb tremor comparisons (i.e., AP-ML, ML-VT, and AP-VT) compared with the levels during the control conditions. In contrast, the addition of the external weights resulted in a decrease in tremor coherence values between limbs.

Effect of Fatigue on Tremor

The impact of fatigue was assessed by examining changes in the amplitude of the tremor over the time course of each trial within each condition. Specifically, each trial was divided into five

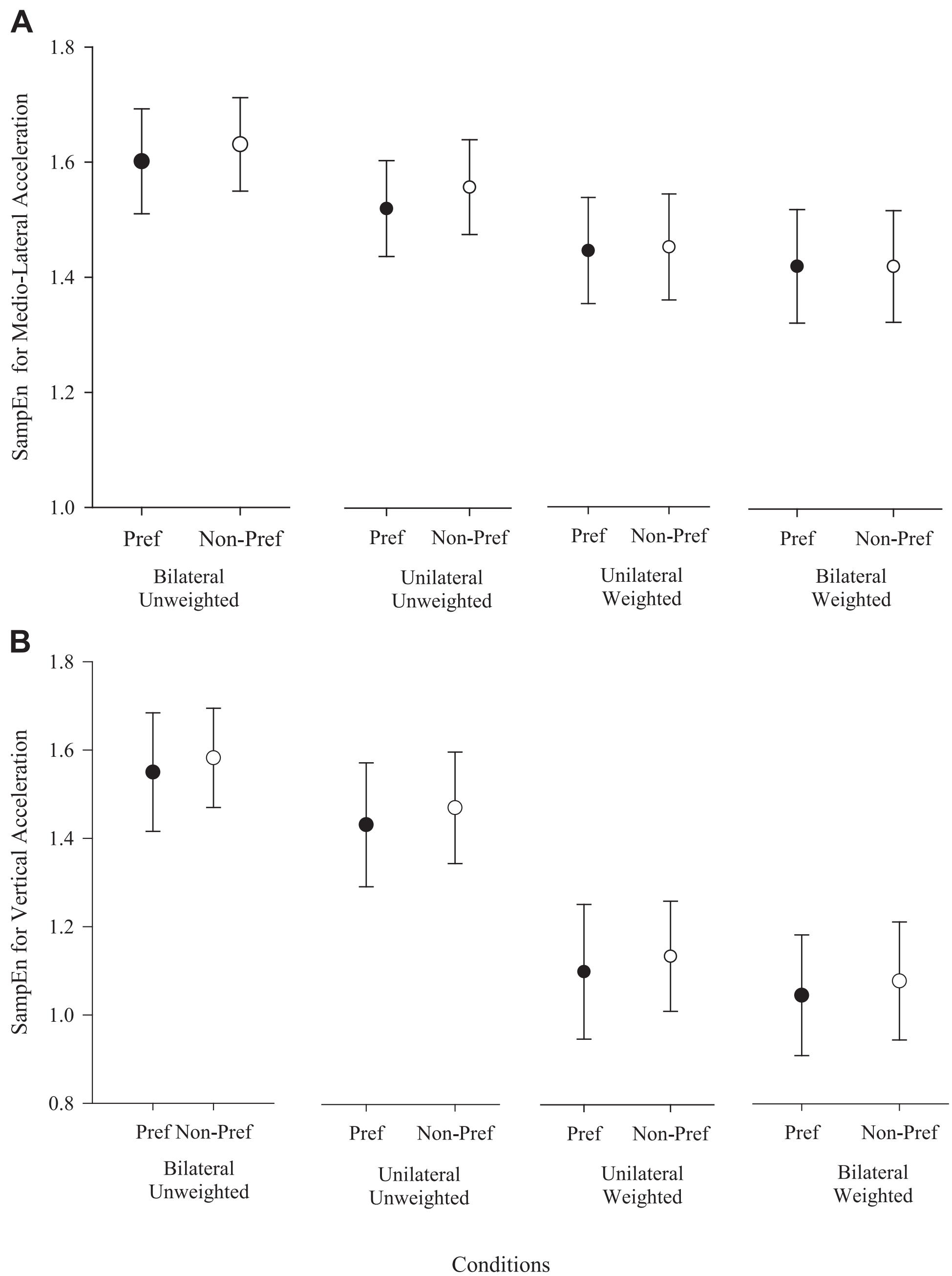

Fig. 4. Plots illustrating average changes in the regularity (SampEn) values of the mediolateral (*A*) and vertical (*B*) index finger tremor across the different task conditions (i.e., bilateral unweighted, unilateral weighted and bilateral weighted). For *A* and *B*, values are shown for both the preferred (Pref) and non-preferred (Non-Pref) limbs for each condition. Error bars represent means ± 1 SD.

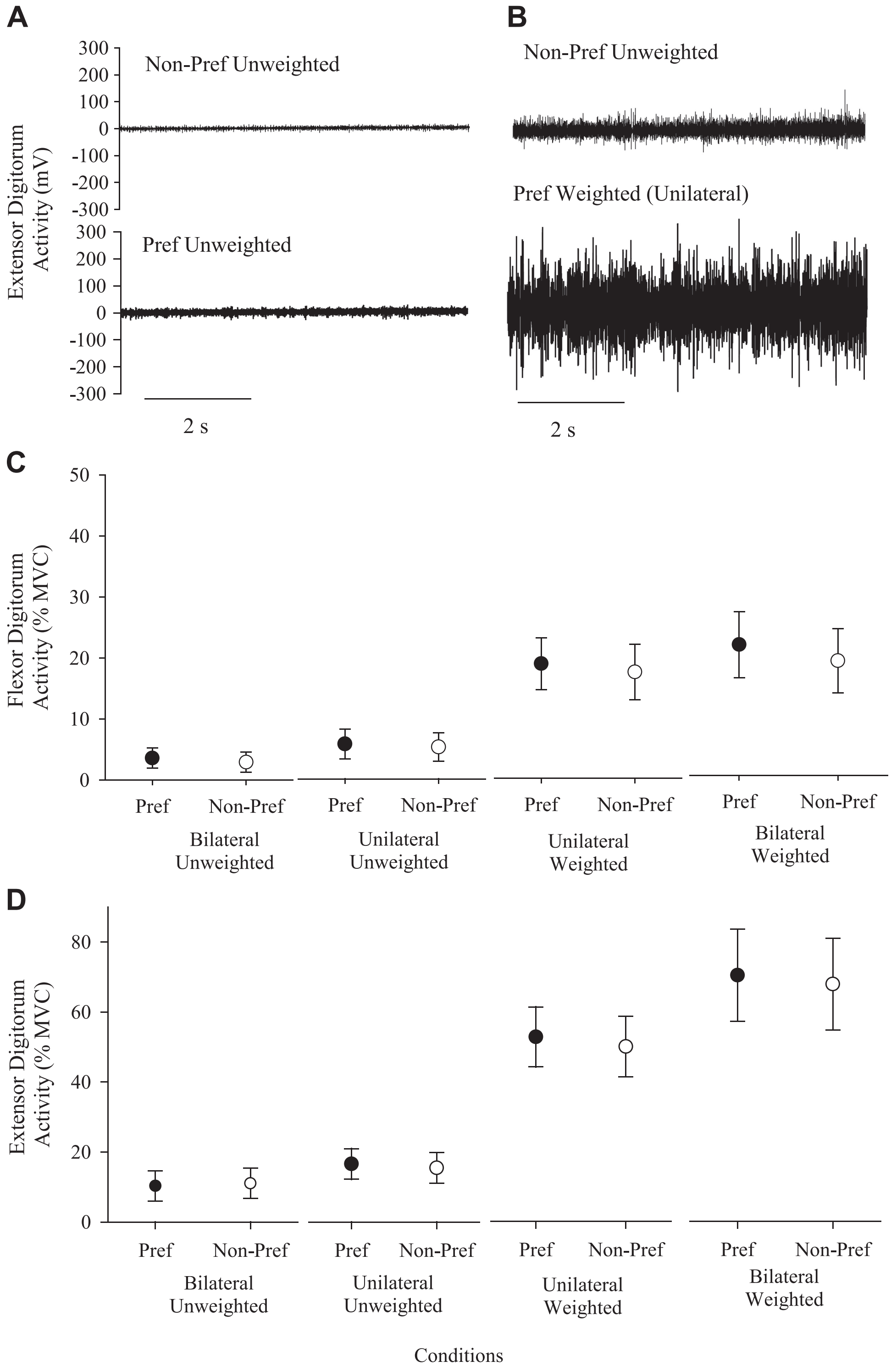

Fig. 5. Representative signals for the EMG activity from extensor digitorum muscle during the unweighted (*A*) and weighted (*B*) tasks for a single subject. Plots illustrating average changes in the EMG activity from the extensor digitorum (*D*) and flexor digitorum (*C*) muscles are shown for the following conditions bilateral unweighted, unilateral weighted, and bilateral weighted) are also shown. MVC, maximal voluntary contraction. Values are shown for both the preferred (Pref) and nonpreferred (Non-Pref) limbs for each condition. Error bars represent means ± 1 SD.

equal sections (i.e., 20% increments). Statistical comparisons were made between the initial period (0–20%) and the final time window (80–100%) of each trial. Figure 7 illustrates the change in the RMS tremor values (AP, ML, and VT) across the various unloaded and loading conditions.

Under unloaded conditions, no significant differences in the RMS amplitude of the tremor signal (in all directions) were observed between the initial and final period of the trial (all $P > 0.05$). For the loaded conditions, the tremor amplitude increased significantly from the initial and final period of the trial. These effects were found for tremor in the VT ($F_{1,17} = 11.87$; $P < 0.01$), ML ($F_{1,17} = 4.91$; $P = 0.004$), and AP directions ($F_{1,17} = 3.64$; $P < 0.05$). No main effects for limb or interaction (limb-by-time section) effects were observed (all $P > 0.05$).

DISCUSSION

This study was designed to examine the dynamics of bilateral index finger tremor in the AP, ML, and VT directions in a

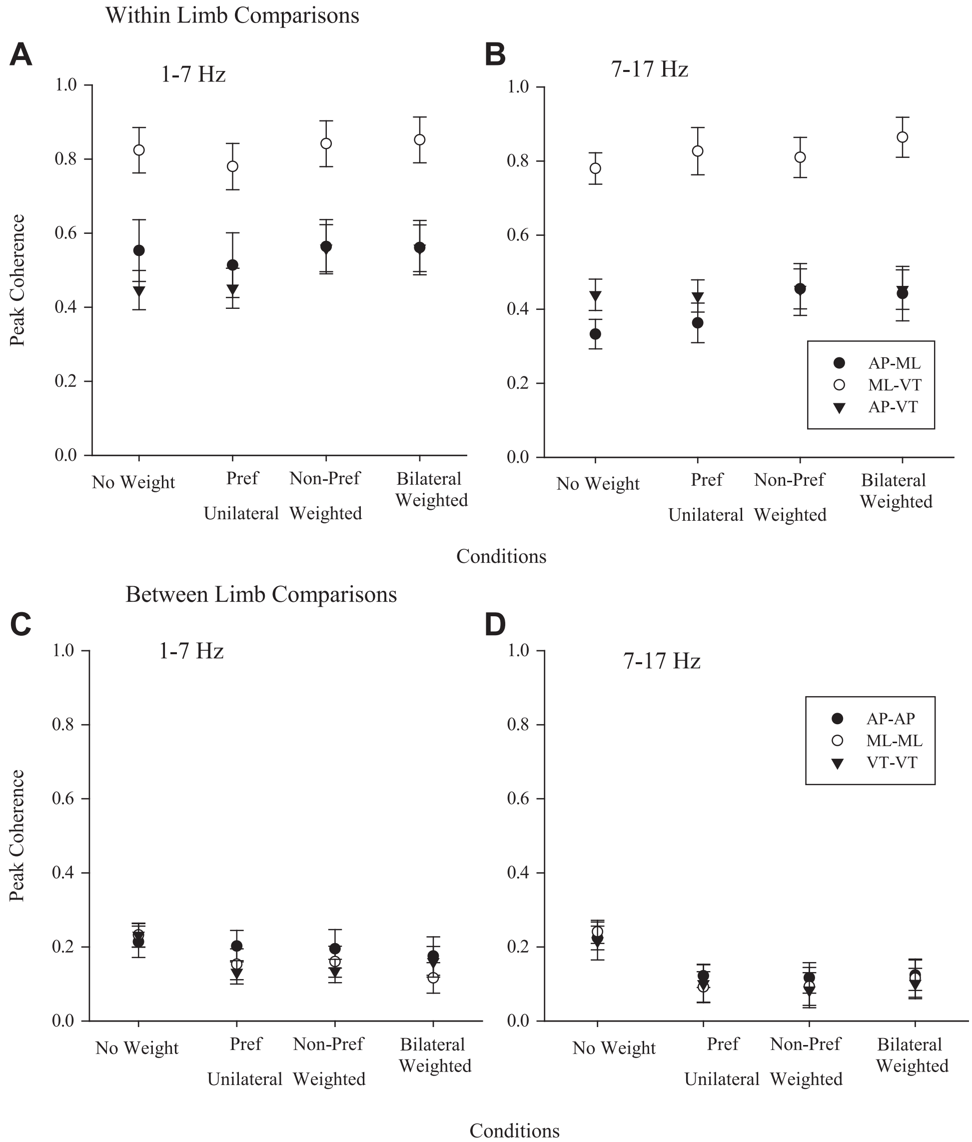

Fig. 6. Plots depicting differences in peak coherence values across the 4 conditions. Within limb comparisons for anterior-posterior (AP)-mediolateral (ML), AP-vertical (VT), and ML-VT tremor are shown between 1 and 7 Hz (*A*) and 7 and 12 Hz (*B*). Between limb coupling for AP-AP, ML-ML, and VT-VT tremor comparisons are also shown between 1 and 7 Hz (*C*) and 7 and 12 Hz (*D*). For the unilateral weighted conditions, coherence values are shown for when the preferred (Pref) and nonpreferred (Non-Pref) limbs were loaded. Error bars represent means ± 1 SD.

cohort of healthy young adults and the effect that holding an external weight until the point of failure has on index finger tremor and forearm muscle activity for both limbs. Overall, the results revealed that for unloaded conditions the tremor in the ML and VT directions was similar in nature and strongly coupled within the same effector. However, no bilateral coupling of the tremor occurred between any plane of motion under the same unloaded conditions. The impact of holding an external load until failure resulted in an increase in neural overflow as reflected in the amplitude of the tremor and forearm muscle activity. Even when only a single limb was loaded, tremor and muscle activity in the contralateral, unloaded limb increased significantly. However, limb loading had no significant impact on the bilateral coupling of tremor.

Dynamics of VT, AP, and ML Tremor

The performance of a postural pointing task is typified by small oscillations or tremor in the limb held against gravity (Elble and Koller 1990; Morrison and Newell 1996; Stiles 1976; 1980; Vaillancourt and Newell 2000). Under these conditions, the amplitude of the tremor observed within a limb is generally greater in the VT direction (Brumlik and Yap 1970; Elble 2005), although associated motion in the AP and ML planes of movement can still be evident (Hong et al. 2008; Kelleran et al. 2016; Pellegrini et al. 2004; Tang et al. 2008). The results of the current study confirm this view whereby, under unweighted (control) conditions, the index finger tremor for both arms exhibited noticeable tremor in all three planes. For this condition, the tremors in the VT and ML directions were similar in amplitude, time-dependent structure (SampEn) and frequency profile, whereby both unloaded limbs exhibit prominent peaks between 2 and 4 Hz and between 8 and 12 Hz.

While there has been considerable research examining the basis for tremor in the VT plane, less emphasis has been placed on assessing tremulous oscillations in the ML direction and its potential origin. The similarity of overall profile of the ML tremor signal to the VT profile combined with the evidence of strong coupling within the 2- to 4-Hz and 8- to 12-Hz bandwidths would indicate that these two components are derived from the same source. The most likely origin for the coupling of ML and VT tremulous oscillations could be mechanical in nature. As the muscles of the forearm and hand produce motion

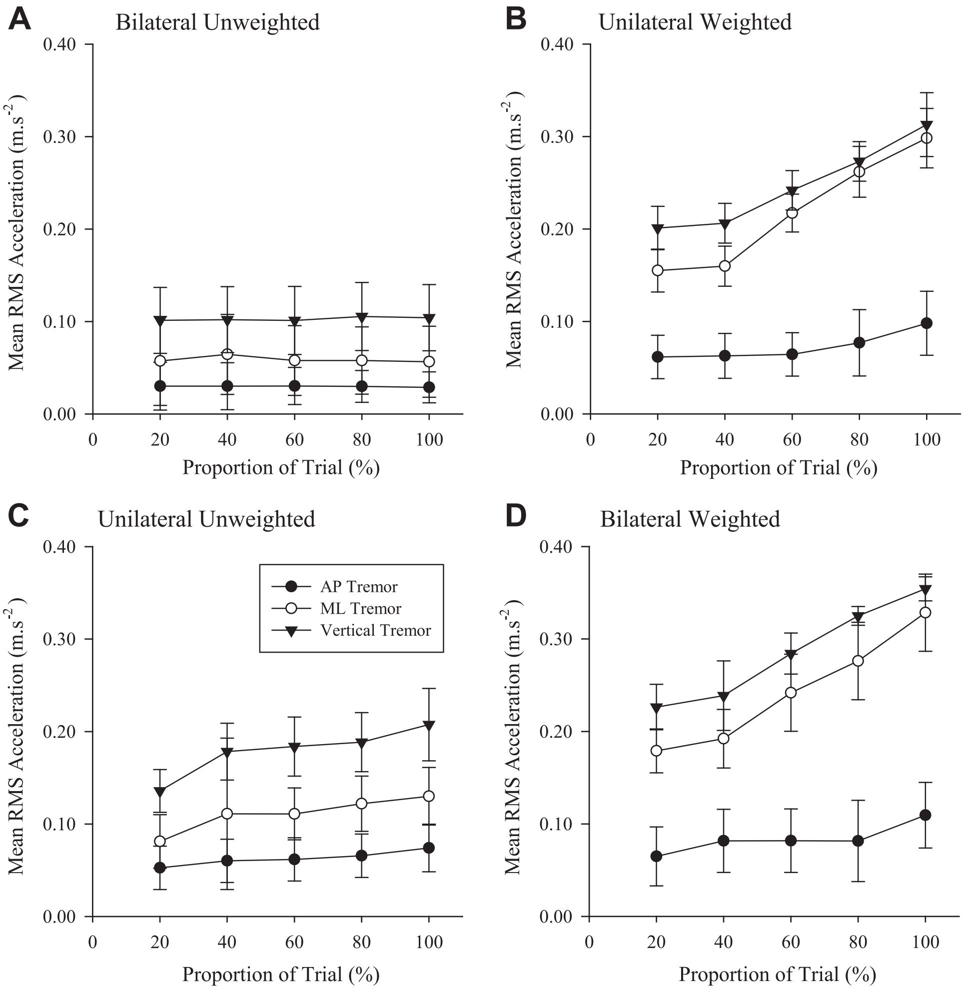

Fig. 7. Plots illustrating average changes in the index finger tremor root mean square (RMS) amplitude across the bilateral unweighted (*A*), unilateral unweighted (*C*), unilateral weighted (*B*) and bilateral weighted) (*D*) conditions. Within each figure, changes in the vertical, mediolateral (ML), and anterior-posterior (AP) tremor are displayed. As there were no significant limb effects, RMS values were collapsed across arms within each of the specified conditions. Error bars represent means ± 1 SD.

in more than one direction, one possibility is that tremor in the VT and ML directions essentially reflects the consequences of activity in the same muscle (Pellegrini et al. 2004). Similarly, the lack of coupling between AP tremor and ML/VT oscillations could also reflect differences in the contribution of mechanical constraints to tremor production. Typically, tremor in the AP direction showed the presence of a single, low peak frequency peak (i.e., <2 Hz) and did not exhibit any significant coupling to either the ML or VT fluctuations.

However, motion in the AP direction was restricted due to the experimental design whereby the forearm rested on a flat surface. In this position, the hand and finger were constrained to eliminate postural sway and other upper limb movements that could have contributed to tremulous motion in the AP direction. While it has been suggested that low-frequency oscillations in the tremor profile could reflect voluntary adjustments using visual feedback to maintain the desired limb position (Kelleran et al. 2016; Miall et al. 1985, 1988; Pellegrini et al. 2004), the position of the forearms and upper limbs here would probably negate the need to effectively control AP oscillations.

Between limbs, there was a remarkable similarity in the nature of the tremor under unloaded conditions even where there was no evidence of any differences in terms of signal amplitude or regularity. Despite this bilateral similarity in appearance, there was no bilateral coupling of tremor in any direction. This finding builds on previous research that has failed to find significant interlimb coupling for VT oscillations (Daneault et al. 2010; Hwang et al. 2006; Morrison and Newell 1999) and extends it by demonstrating that tremor in the AP and ML directions is similarly unrelated to oscillations in the same plane within the contralateral limb. Although this pattern appears to be preserved, our focus here was to examine whether stressing the system, in this case loading a limb until task failure, could potentially lead to increased coupling of tremor between limbs.

Effect of External Loading on Three-Dimensional Index Finger Tremor

Irrespective of whether a single or both index fingers were loaded simultaneously, the time to failure was similar. On average, the time to failure was between 1 min 22 s to 1 min 34 s across the loading conditions. Given that the duration of the control trials was longer (i.e., 2 min), we can be confident that the tremor and EMG changes are associated with fatigue caused by holding the load until failure. As expected, tremor amplitude increased as a function of the fatigue caused by having to hold the external weight until failure. However, loading a single limb also led to an increase in the tremor (in all directions) and EMG responses in the unweighted index finger. Interestingly, the change in the contralateral tremor was preserved even though there was no evidence of any increase in coupling (as assessed by changes in coherence) of the tremor between the two limbs.

Previous research has consistently demonstrated that fatiguing a single limb leads to systematic increases in the tremor amplitude within that limb (Morrison et al. 2005; Palmer 1991; Saxton et al. 1995). This response has been observed despite methodological differences regarding how fatigue was induced. For example, fatigue has been induced by performing isotonic contractions to failure (Morrison et al. 2005; Morrison and Sosnoff 2010; Saxton et al. 1995), maintaining a sustained contraction at a percentage of a person's MVC (Arihara and Sakamoto 1999; Huang et al. 2007), holding a postural position against an external load (Ebenbichler et al. 2000; Hwang et al. 2006), or simply holding the limb against gravity with no external load for an extended period of time (Palmer 1991). In all these cases, the outcome with regards to the tremor is remarkably similar, in that there is an increase in amplitude and/or decrease in the modal frequency values. In the current study, loading a limb resulted in an increase in the amplitude (i.e., peak power and mean RMS) of the tremulous oscillations in all three planes with a corresponding decrease in the frequency at which the tremor peaks were found (i.e., 2–4 Hz and 8–12 Hz for VT and ML tremor, 1–3 Hz for the AP tremor).

The impact of loading on limb tremor was not restricted to increases in signal amplitude but also reflected by a change in the regularity of the tremor signals. Under unloaded conditions, the SampEn results revealed that the ML (range 1.60–1.63) and VT (1.55–1.59) tremor signals were similar in structure and became more regular (i.e., SampEn values decreased) during the loaded conditions. This was a general pattern of decline with fatigue that is consistent with that reported previously for isometric knee extension tasks (Pethick et al. 2015, 2018). However, the effect of adding an external load had the greatest effect on the regularity of the VT tremor responses, which showed a greater loss of complexity (i.e., decreased SampEn) compared with the changes seen for tremor in the ML direction. The basis for the increases in both tremor and EMG amplitude, coupled with the decline in tremor regularity, is probably related to changes in muscle firing rates with fatigue. It has been suggested that with the decline in fast motor unit involvement during fatiguing actions (Enoka 1995; Enoka and Stuart 1992), the more regular tremor signal reflects the consequences of increased output from a smaller proportion of the overall motor unit pool (Pethick et al. 2015). Declines in signal regularity have also been linked with increases in the lower frequency tremor component (i.e., 2–4 Hz), which may be related to increased control over the respective limb (Morrison and Newell 1996). Consequently, a decline in signal complexity could reflect any increased volitional contribution during the loading conditions to achieve the task goal of maintaining the desired postural position.

It is of interest that, under conditions where a single limb was weighted, the amplitude of the tremor and muscle activity (both the flexors and extensors) in the contralateral (unweighted) limb also increased while the complexity (SampEn) of the tremor decreased. This change in the unweighted limb occurred even though there was no evidence of any increase in coupling between the two limbs. Previous studies (Morrison et al. 2005; Morrison and Sosnoff 2010) have reported a similar finding although the means by which fatigue was induced differed in that adults performed wrist flexion/extension movements with a weight to fatigue and the tremor was recorded postexercise. In the current study, the increases were seen during the performance of the fatiguing action, indicating that the method of how fatigue was induced is unlikely to be the determining factor in the responses observed.

A Potential Basis for Tremor-Related Cross-Limb Effects

Our finding of increased tremor amplitude and muscle activity in the contralateral (unloaded) limb without concomitant increases in between-limb coupling provides insight to the mechanism of crossed-limb effects. A long-held explanation for the emergence of unintended activity in the contralateral limb is that activity in motor cortex areas contralateral to the contracting muscle is transferred to the same motor areas in the ipsilateral cortex (Bodwell et al. 2003; Ruddy et al. 2017; Zijdewind and Kernell 2001; Zijdewind et al. 1998). Although the exact cortical mechanism of crossed-limb effects is yet to be revealed, the most prevalent condition for crossed effects is the performance of strong brief contractions or prolonged fatigue-inducing contractions such as those evident in the current study. Indeed, previous studies have reported that during unilateral actions with either a high force requirement and/or following fatigue a spread or overflow of neural activity to homologous muscles of the contralateral arm can occur (Kavanagh et al. 2016; Ruddy et al. 2017; Zhou 2000; Zijdewind and Kernell 2001; Zijdewind et al. 1998). It should be noted, however, that while cortical mechanisms may play a role in transferring motor signals to the opposite limb, the lack of coherence between limbs suggests that the descending motor commands to each limb were not identical. As such, activity in ipsilateral cortex may have initiated nonspecific motor activity in pathways that project to the nonactive limb, and then spinal cord mechanisms increased the gain of motor neuron activity in the nonactive limb to enhance muscle and tremor activity.

Descending neural drive contributes to ~40% of muscle contraction, with the remaining proportion arising from the simultaneous release of serotonin in the spinal cord (Heckman et al. 2009). During strong contractions, serotonergic pathways that project from the brainstem to the spinal cord release serotonin onto motor neurons, which increases the excitability of motor neurons. As well as altering the membrane threshold of the motor neurons, activation of serotonin receptors promotes activity of voltage-gated persistent inward currents and allows repetitive firing of motor neurons (Harvey et al. 2006; Li et al. 2007). Therefore, it is plausible that a small increase in the voluntary neural drive to the nonactive limb could produce changes in muscle activity and tremor providing that serotonin was released onto the motor neurons of both limbs.

A recent study by Wei et al. (2014) supports this mechanism, whereby a series of experiments were performed that modulated motor neuron gain via large contractions in contralateral effectors. In this study, the excitatory nature of the serotonergic system was first demonstrated by increasing the amplitude of tendon vibration reflexes and stretch reflexes by enhancing the availability of endogenous serotonin with escitalopram. Similar to the current study, they then performed contractions with one limb and observed increases in index finger fluctuations in the opposite limb. It was revealed that these index finger fluctuations in the opposite, minimally active limb, can be decreased with the serotonin antagonist cyproheptadine and increased with the selective serotonin reuptake inhibitor paroxetine. Our results are consistent with this spinal cord mechanism as prolonged limb loading most likely increased serotonergic drive to both sides of the hemicord and even small amounts of descending drive to the unloaded limb would be reflected in enhanced muscle activity and tremor amplitude.

Future considerations should address the time-dependent effects of the loading interventions on limb tremor. By assessing changes in the muscle activity and tremor over the course of a single fatiguing trial, further insight would be gained as to the how the signal change over time. Designing protocols to elucidate the similarities between the ML and VT tremor would also provide insight as to the origins of these components of tremor. Finally, given the restrictions placed on any tremor in the AP direction, it would be useful to assess the dynamics of the tremor component under conditions where the distal segments were free to move (i.e., when the subject was standing). This would also allow assessment of any potential coupling between AP tremor and other physiological events such as postural sway. Such investigations may enhance clarity to the origin of the AP tremulous oscillations.

Conclusions

Overall, the results of the current study revealed that tremor in the ML and VT directions was strongly coupled in both the 2- to 4-Hz and 8- to 12-Hz bands, implying that these two tremor forms are directly related and probably derived from mechanical sources. In contrast, tremor in the AP direction, which was at a lower frequency, is more likely to be a separate tremulous event only weakly associated with the other directional tremor fluctuations. Loading a single limb led to increases in VT, AP, and ML tremor amplitude and muscle activity across both limbs, although the interlimb coupling of tremor was not affected. The contralateral increases in tremor and muscle activity reflect the consequence of a neural overflow effect. The lack of any bilateral coupling of tremor, however, suggests that the independence of postural tremor generation in healthy adults is preserved under fatigue conditions.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

S.M., J.J.K., and K.N. conceived and designed research; S.M. performed experiments; S.M. analyzed data; S.M., J.J.K., and K.N. interpreted results of experiments; S.M., J.J.K., and K.N. prepared figures; S.M., J.J.K., and K.N. drafted manuscript; S.M., J.J.K., and K.N. edited and revised manuscript; S.M., J.J.K., and K.N. approved final version of manuscript.

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