Bilateral tremor responses to unilateral loading and fatiguing muscle contractions

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Submitted 28 March 2013; accepted in final form 30 April 2013

Kavanagh JJ, Cresswell AG, Sabapathy S, Carroll TJ. Bilateral tremor responses to unilateral loading and fatiguing muscle contractions. J Neurophysiol 110: 431–440, 2013. First published May 1, 2013; doi:10.1152/jn.00228.2013.—Although physiological tremor has been extensively studied within a single limb, tremor relationships between limbs are not well understood. Early investigations proposed that tremor in each limb is driven by CNS oscillators operating in parallel. However, recent evidence suggests that tremor in both limbs arises from shared neural inputs and is more likely to be observed under perturbed conditions. In the present study, postural tremor about the elbow joint and elbow flexor EMG activity were examined on both sides of the body in response to unilateral loading and fatiguing muscle contractions. Applying loads of 0.5, 1.0, 1.5, and 3.0 kg to a single limb increased tremor and muscle activity in the loaded limb but did not affect the unloaded limb, indicating that manipulating the inertial characteristics of a limb does not evoke bilateral tremor responses. In contrast, maximal-effort unilateral isometric contractions resulted in increased tremor and muscle activity in both the active limb and the nonactive limb without any changes in between-limb tremor or muscle coupling. When unilateral contractions were repeated intermittently, to the extent that maximum torque generation about the elbow joint declined by 50%, different tremor profiles were observed in each limb. Specifically, unilateral fatigue altered coupling between limbs and generated a bilateral response such that tremor and brachioradialis EMG decreased for the fatigued limb and increased in the contralateral nonfatigued limb. Our results demonstrate that activity in the nonactive limb may be due to a “spillover” effect rather than directly coupled neural output to both arms and that between-limb coupling for tremor and muscle activity is only altered under considerably perturbed conditions, such as fatigue-inducing contractions.

Physiological tremor; crossed effect; maximum voluntary contraction

Physiological tremor has been attributed to the mechanical resonance of a body segment, peripheral stretch reflex loops, motor unit synchronization, motor unit discharge properties, and rhythmic activity arising from the central nervous system (CNS) (Elble 1996; McAuley and Marsden 2000). Although extensively studied within a single limb, tremor relationships between limbs are not well understood. Early investigations found few relationships between limbs and concluded that the tremor in each limb was driven by parallel CNS oscillators (Marsden et al. 1969a, 1969b). However, these conclusions were drawn from simple assessments of index finger tremor, without internal or external perturbation. More recent investigations that have explored the effects of perturbing limb mechanics have revealed significant between-limb relationships. In particular, splinting a single limb to restrict joint motion, and inducing neuromuscular fatigue in a single limb, has the effect of increasing tremor and muscle activity in both the perturbed and nonperturbed limbs (Morrison et al. 2005; Morrison and Newell 1999). Collectively, the aforementioned studies suggest that physiological tremor is relatively independent in each limb under normal conditions. However, when inherent patterns of coordination are manipulated in a single limb, bilateral interactions increase and tremor is modified in the contralateral limb (Boonstra et al. 2008).

Although it is unknown whether perturbing the mechanical component of tremor will induce tremor changes in the contralateral limb, within-limb mechanisms have been characterized in detail. During maintained postures, motor unit activity combined with musculotendon and viscoelastic filtering properties cause the limb to oscillate at a natural resonance frequency (Allum et al. 1978; Elble and Randall 1978; Lakie et al. 2012; Stiles and Randall 1967). This rhythm feeds back to spinal cord circuitry, which presumably modulates tremor through monosynaptic reflexes (Hagbath and Young 1979). The mechanical resonance component of tremor differs according to limb size. For example, the frequency of tremor occurs between 15 and 30 Hz for the finger (Stiles and Randall 1967), between 8 and 12 Hz for the hand (Elble and Randall 1978; Lakie et al. 1986), and between 3 and 5 Hz for the forearm (Fox and Randall 1970; Joyce and Rack 1974). While these peripheral mechanisms of tremor remain relatively fixed, applying an inertial load to the limb can effectively decrease the resonant frequency of oscillation and increase oscillation amplitude (Halliday et al. 1999; Homberg et al. 1987). Such changes in limb kinematics have been argued to modify reflex responsiveness in the agonist motor neuron pool via altered activity in muscle afferent pathways (Maluf et al. 2007; Maluf and Enoka 2005; Pascoe et al. 2013). As such, limb loading offers a method to selectively perturb a subset of tremor mechanisms and reveal whether the mechanical component of limb tremor plays a role in bilateral tremor relationships.

The simple act of volitionally increasing muscle activity can increase tremor amplitude of the relevant limb segment. During sustained submaximal contractions, excitatory drive to the motor neuron pool progressively increases and is paralleled by progressive increases in EMG and tremor in that limb (Lösch et al. 1994, 1996). However, if maximal contractions are performed, an alternative pattern of tremor should be observed. That is, EMG will be immediately high, and presumably tremor amplitude would be maximal. It is well known that strong unilateral contractions generate cortical activity both contralateral and ipsilateral to the contracting muscle (Hess et al. 1986; Lee et al. 2010), and activity tends to emerge in the contralateral homologous muscles (Shinohara et al. 2003; Zi-
As the magnitude of these crossed effects is related to the force of contraction (Hortobágyi et al. 2003; Perez and Chohen 2008), one would predict that brief maximal efforts would be the condition most likely to generate muscle and tremor responses in the contralateral limb. Surprisingly, the effects of strong muscle contractions on contralateral limb tremor are yet to be determined.

While a body of knowledge has developed regarding bilateral muscle activity, few studies have examined the crossed effects of tremor associated with repeated unilateral contractions. Postural tremor has been quantified for bilateral pointing (arms held against gravity with index fingers extended) following single-limb dumbbell-weighted full-range wrist extensions. Fatigue-inducing wrist extensions of a single limb [weight set at 50% maximum voluntary contraction (MVC)] cause postexercise increases in extensor digitorum activity and index finger postural tremor in both limbs (Morrison et al. 2005; Morrison and Sosnoff 2010). Furthermore, if wrist extensions are continued to task failure, postural tremor systematically increases for both limbs during recovery (Morrison et al. 2005). As such, there appears to be a postexercise increase in neural drive to the target and nontarget motor neuron pools that results in enhanced tremor. However, it is yet to be determined how tremor is affected in the contralateral limb during fatiguing muscle contractions, and it is also unknown how the homologous agonist muscles interact in the contralateral limb to produce the tremor response.

The purpose of this study was to examine forearm acceleration (tremor) and elbow flexor EMG activity on both sides of the body when a controlled posture was adopted. It was hypothesized that applying loads to a single limb would increase the amplitude and decrease the 3-Hz frequency of tremor for the loaded limb and have no effect on tremor or the loaded limb. The degree of acceleration and EMG coupling between limbs would reflect the extent to which any additional tremor in the contralateral limb is generated directly by increased oscillatory neural drive to the fatigued limb.

METHODS

Subjects and Ethical Approval

Twelve healthy male subjects (age: 23 ± 4 yr, height: 183 ± 8 cm, body mass: 81 ± 7 kg; all right hand preferred) with no history of neurological or recent musculoskeletal injury were recruited from the university community. No subject had participated in resistance training in the 12 mo prior to testing, and only 3 of 12 subjects had any formal history of resistance training. Participants were asked to abstain from caffeine, alcohol, exercise, or any form of CNS stimulant or depressant for at least 6 h prior to testing. Written informed consent was obtained before testing. All experimental procedures were approved by the Griffith University Human Research Ethics Committee, and experiments were performed in accordance with the Declaration of Helsinki.

Study Design

Two experiments were performed to examine the bilateral nature of physiological tremor about the elbow joint. The first experiment examined the effects of unilateral loading on bilateral tremor, and the second experiment examined the effects of unilateral fatigue on bilateral tremor.

Bilateral Tremor Measurement

Subjects sat in a firm-back adjustable chair so that the trunk remained upright and the arms could be held in a comfortable position. The elbows were flexed to 90°, and the humerus remained vertical in the sagittal plane and slightly abducted in the frontal plane. Joint angles were verified with a goniometer. Solid adjustable benches were placed underneath each elbow to create a support surface for the olecranon. This setup allowed motion about the elbow joint to be examined when only the forearm was held against gravity (Fig. 1). Custom-designed lightweight splints were placed on the hands to ensure that forearm muscle activity was minimized and a neutral joint

![Fig. 1. Experimental setup for bilateral tremor assessment (left), unilateral loading in experiment 1 (bottom right), and the unilateral fatigue task in experiment 2 (top right). With each setup, bilateral responses could be measured during the unilateral tasks.](http://jn.physiology.org/Downloadedfromhttp://jn.physiology.org/)
position was maintained throughout testing. The splints also ensured that the wrist was held midway between supination and pronation for all testing, as changes to supination and pronation can substantially influence torque production during elbow flexion (Buchanan et al. 1989; Jamison and Caldwell 1993).

Acceleration and surface EMG data were obtained from both limbs while in this experimental posture. Lightweight NL261 uniaxial accelerometers (mass: 2.55 g, range: ±1.7 G; Digitimer) were attached over the head of the radius so that the sensing axis was aligned with the global vertical and motion about the elbow joint could be measured. The accelerometers were calibrated by zero balancing in DC mode on a level surface prior to testing in AC mode. Raw acceleration data were amplified through a NL109 bridge amplifier (Digitimer).

EMG activity was measured for elbow flexors and extensors. After skin preparation, bipolar Ag/AgCl electrodes (Kendall Arbo) were placed distal to the motor point of biceps and brachioradialis and over the lateral head of triceps. Electrodes were oriented with the underlying muscle fibers and spaced with an interelectrode distance of 24 mm. A reference electrode was placed over the acromion process. EMG power spectra were monitored during subject preparation, and electrode placement was adjusted if clear data could not be obtained. Surface EMG were amplified 10,000 times with an NL844 amplifier (Digitimer) and band-pass filtered at 2–300 Hz (NL135, NL144; Digitimer) during data acquisition. Impedance was kept below 5 kΩ at all electrode sites. All accelerometer and EMG data were acquired at 2 kHz with a 16-bit Power 1401 interface and custom Spike2 software (Cambridge Electronic Design).

Experiment 1. Unilateral Loading and Bilateral Tremor

Three 20-s trials of bilateral tremor were collected to provide baseline data (normal physiological tremor) before fixed loads were added to the preferred limb. Loads of 0.5, 1.0, 1.5, and 3.0 kg were strapped to the forearm 3 cm proximal to the head of the radius (Fig. 1). The order of loading was randomized, and sufficient rest was given between trials to ensure that fatigue did not develop. Subjects were continually encouraged to maintain 90° of elbow flexion for both limbs and keep their nonloaded limb relaxed throughout testing. Acceleration and EMG were monitored in real time to ensure that the subject was relaxed. Three 20-s trials were performed for each loading condition.

Experiment 2. Unilateral Fatigue and Bilateral Tremor

Nine subjects participated in the second experiment. Before subjects undertook the fatigue task, M-wave recruitment curves and MVC were established for the preferred limb of each subject. M-wave recruitment curves were used to determine maximal M-wave amplitude (M-max) of biceps and brachioradialis. Ag/AgCl cathodes were placed over the motor points of biceps brachii and brachioradialis, and anodes were placed over the bicipital tendon and a brachioradialis tendon, respectively. Electrical stimulation was delivered to each muscle with separate constant-current stimulators (DS7AH; Digitimer), and M-wave responses were measured from EMG of biceps and brachioradialis. Stimulation was gradually increased until the peak-to-peak M-wave amplitude did not increase with further increases in current (0.2-ms pulse, 80–195 mV).

Three 20-s trials of bilateral tremor were collected to provide baseline data before the unilateral fatigue task was performed. The fatigue task was an intermittent MVC protocol in which the subject was relaxed. Three 20-s trials of bilateral tremor were collected to provide baseline data (normal physiological tremor) before fixed loads were added to the preferred limb. Loads of 0.5, 1.0, 1.5, and 3.0 kg were strapped to the forearm 3 cm proximal to the head of the radius (Fig. 1). The order of loading was randomized, and sufficient rest was given between trials to ensure that fatigue did not develop. Subjects were continually encouraged to maintain 90° of elbow flexion for both limbs and keep their nonloaded limb relaxed throughout testing. Acceleration and EMG were monitored in real time to ensure that the subject was relaxed. Three 20-s trials were performed for each loading condition.

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Three 20-s trials of bilateral tremor were collected to provide baseline data before the unilateral fatigue task was performed. The fatigue task was an intermittent MVC protocol in which the subject adopted the same posture described in Bilateral Tremor Measurement. Isometric elbow flexion force was measured for the preferred limb with a Xtran 1-kN S-beam load-cell transducer (Applied Measurements) connected to a solid bench and a firm strap attached 3 cm proximal to the head of the radius (Fig. 1). A fatigue set consisted of four 2-s MVCs, with 1 s of rest between contractions (Fig. 2). A monitor placed in front of the subject produced a visual cue to indicate the timing of contractions. On the third and fourth contractions in the set, paired supramaximal M waves (0.02-s interval, 0.2-ms pulses at 130% M-max) were evoked in the brachioradialis and biceps, respectively. At the completion of the fatigue set, a rest period of 3 s was taken in which paired supramaximal M waves were again evoked for the brachioradialis and biceps. Subjects were continually encouraged to relax their nonexercising limb during testing. Fatigue sets were repeated until the subject could not maintain a torque output higher than 50% of what he could produce in his first set.

Data Analysis

All data analyses were performed with custom MATLAB software (MathWorks, v7.7.0, R2008b). Acceleration data were low-pass filtered with a dual-pass fourth-order Butterworth filter with a cutoff frequency of 40 Hz. Filtered acceleration and raw EMG data were converted to root mean square (RMS) to examine the amplitude of

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forearm tremor and elbow joint muscle activity, respectively. Acceleration and EMG data collected in experiment 1 were examined in the frequency domain with Welch’s averaged periodogram method. The power in the filtered acceleration signal was examined in the 2–8 Hz bandwidth, which contains distinct frequency content for the mechanical component of postural tremor for the forearm (Fox and Randall 1979). The frequency of peak power between 2 and 8 Hz was calculated for each experimental task. For EMG frequency-domain analysis, raw EMG data were full-wave rectified and then low-pass filtered at 40 Hz (termed demodulated EMG; Eble and Randall 1976; Fox and Randall 1979; Joyce and Rack 1974; Matthews and Muir 1980). Power spectral analysis was then performed on the demodulated EMG signal, and the frequency of peak power in the bandwidth of 8–12 Hz was identified.

Cross correlation and cross approximate entropy (ApEn) analyses were performed to examine coupling relations between limbs. As tremor coupling is dynamic and may continually change throughout each trial, coupling analyses in experiment 1 were performed on 10 consecutive 1-s epochs for the middle portion of each trial. From the cross correlation analysis, the peak correlation coefficient and the phase difference associated with the peak correlation coefficient (time lag between oscillating signals) were used as a measure of the degree of coupling between forearm acceleration, demodulated biceps EMG, and demodulated brachioradialis EMG. For the purpose of this study, the time lags between limbs are expressed as absolute values.

Cross ApEn was applied to paired acceleration and demodulated EMG data. This analysis quantified the degree of synchrony, or frequency similarity between limbs, by calculating the logarithmic likelihood that a short pattern of data in one signal will fall within a frequency similarity between limbs, by calculating the logarithmic likelihood that a short pattern of data in one signal will fall within a frequency similarity between limbs, by calculating the logarithmic likelihood that a short pattern of data in one signal will fall within a frequency similarity between limbs, by calculating the logarithmic likelihood that a short pattern of data in one signal will fall within a frequency similarity between limbs, by calculating the logarithmic likelihood that a short pattern of data in one signal will fall within a frequency similarity between limbs, by calculating the logarithmic likelihood that a short pattern of data in one signal will fall within a frequency similarity between limbs, by calculating the logarithmic likelihood that a short pattern of data 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indicated that the combined changes of LOA and RT for brachioradialis and biceps explained 94% of variance for the decline in elbow flexion torque ($P/11005 \leq 0.03$).

**Bilateral tremor during contractions of the fatigue task.** Tremor profiles were altered for both limbs while performing the unilateral fatigue task, whereby force tremor was assessed for the limb contracting against the load cell and postural tremor was assessed in the contralateral limb when in the experimental posture. During contractions of the fatigue task, the standard deviation of torque significantly decreased from the first fatigue set to the last fatigue set ($P/11005 \leq 0.02$). Acceleration amplitude increased from baseline during the first set for the nonexercising limb ($P/11021 \leq 0.01$) and remained greater than baseline until the final fatigue set ($P/11005 \leq 0.04$; Fig. 5). From the first to the final fatigue set, acceleration significantly increased for the nonexercising limb ($P/11005 \leq 0.04$).

Muscle activity was also altered for both limbs during contractions of the fatigue task. EMG amplitude increased from baseline ($P/11005 \leq 0.04$).

**Table 1.** *Between-limb coupling during unilateral loading task*

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>0.5 kg</th>
<th>1.0 kg</th>
<th>1.5 kg</th>
<th>3.0 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cross correlation coefficient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forearm acceleration</td>
<td>0.36</td>
<td>0.32–0.39</td>
<td>0.37</td>
<td>0.33–0.40</td>
<td>0.41</td>
</tr>
<tr>
<td>Biceps EMG</td>
<td>0.81</td>
<td>0.80–0.82</td>
<td>0.81</td>
<td>0.80–0.82</td>
<td>0.82</td>
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<tr>
<td>Brachioradialis EMG</td>
<td>0.83</td>
<td>0.82–0.84</td>
<td>0.84</td>
<td>0.83–0.85</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Cross correlation phase, ms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Forearm acceleration</td>
<td>63</td>
<td>50–76</td>
<td>71</td>
<td>57–85</td>
<td>57</td>
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<tr>
<td>Biceps EMG</td>
<td>11</td>
<td>9–14</td>
<td>14</td>
<td>9–20</td>
<td>12</td>
</tr>
<tr>
<td><strong>Cross ApEn</strong></td>
<td></td>
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<tr>
<td>Forearm acceleration</td>
<td>0.14</td>
<td>0.12–0.17</td>
<td>0.12</td>
<td>0.10–0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>Biceps EMG</td>
<td>0.24</td>
<td>0.23–0.25</td>
<td>0.25</td>
<td>0.24–0.26</td>
<td>0.25</td>
</tr>
<tr>
<td>Brachioradialis EMG</td>
<td>0.25</td>
<td>0.24–0.26</td>
<td>0.24</td>
<td>0.23–0.25</td>
<td>0.25</td>
</tr>
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ApEn, approximate entropy; CI, confidence interval.

J Neurophysiol  •  doi:10.1152/jn.00228.2013  •  www.jn.org
baseline during the first set ($P < 0.01$) and remained greater than baseline until the final set ($P < 0.02$; Fig. 5) for both the brachioradialis and biceps of the exercising limb. Similarly, EMG increased during the first set for the nonexercising limb brachioradialis and biceps (both $P < 0.02$) and remained greater than baseline until the final set (both $P < 0.01$). Brachioradialis EMG followed a profile similar to that of tremor, where EMG decreased for the exercising limb ($P = 0.04$), and increased for the nonexercising limb ($P = 0.04$) from the first to the final fatigue set.

Fatigue-related differences were identified for between-limb coupling. Peak cross correlation coefficients significantly decreased from the first to the last fatigue set for biceps EMG ($P = 0.01$) and brachioradialis EMG ($P = 0.03$; Table 2). Furthermore, the phase lag increased between limbs for biceps EMG ($P = 0.04$) and decreased between limbs for brachioradialis EMG ($P = 0.04$) from the first to the last fatigue set. The reduced phase lag in brachioradialis activity coincided with increased synchrony in between-limb tremor. That is, tremor cross ApEn decreased from the first to the last fatigue set ($P = 0.02$), indicating that synchrony in torque for the exercising limb and acceleration of the nonexercising limb increased with fatigue.

**Bilateral tremor during rest intervals of the fatigue task.** Similar to the contraction phase, tremor profiles during the rest intervals of the unilateral fatigue task were altered for both limbs. Acceleration amplitude for the exercising limb increased from baseline during the first set and remained greater than baseline until the final fatigue set ($P = 0.04$; Fig. 6). Acceleration amplitude for the nonexercising limb was greater for the final fatigue set (both $P < 0.05$). Muscle activity was also altered for both limbs during the rest intervals. EMG amplitude was greater than baseline during the rest interval of the first set for the exercising limb biceps and nonexercising limb brachioradialis ($P < 0.01$) and remained greater than baseline until the final set ($P < 0.01$; Fig. 6).

Compared with baseline, peak cross correlation coefficients were lower for the rest interval of the last fatigue set for biceps EMG ($P = 0.03$) and brachioradialis EMG ($P = 0.02$; Table 2). Furthermore, cross ApEn decreased from baseline to the rest interval of the last fatigue set for biceps EMG ($P = 0.01$) and brachioradialis EMG ($P = 0.02$), indicating that synchrony between muscle activity in each limb increased with fatigue. Although nonsignificant, the reduction in between-limb phase lag for biceps and brachioradialis EMG followed the same pattern of increased synchrony between these muscles.

**DISCUSSION**

Two experiments were performed to examine the bilateral nature of physiological tremor about the elbow joint. The main findings of these experiments were that 1) loading a single limb did not affect tremor or muscle activity in the unloaded limb, 2) maximal-effort unilateral contractions induced tremor and muscle responses in the contralateral nonactive limb without changing coupling between the limbs, and 3) unilateral fatigue affected coupling between limbs and generated a bilateral response such that tremor and brachioradialis EMG decreased for the fatigued limb and increased in the contralateral nonfatigued limb.

**Unilateral Loading Had a Limited Effect on the Contralateral Limb**

Applying loads from 0.5 to 3.0 kg altered tremor and muscle activity in the loaded limb but had no significant effect on the contralateral unloaded limb. As expected, tremor amplitude...
Maximal-Effort Unilateral Contraction Induced Bilateral Tremor and Muscle Responses

During the first set of the fatigue task, tremor and muscle responses to a brief maximal-effort isometric contraction were assessed in a nonfatigued state. In agreement with previous investigations, generation of large torques about a single joint was accompanied by increased force tremor and muscle activity in the limb performing the task (Allum et al. 1978; Löscher et al. 1994, 1996; Shinohara et al. 2003; Zijdewind et al. 2006; Zijdewind and Kernell 2001). Also consistent with previous work, it appears that strong isometric elbow flexion cannot be performed without increasing muscle activity in the contralateral homologous muscle(s) (Zijdewind et al. 2006). Brachioradialis and biceps activity increased from baseline levels in both limbs during the maximal contraction, which was accompanied by clear increases in the amplitude of forearm tremor for both limbs. Given that the LOA for brachioradialis and biceps was high, and the contraction likely exceeded the recruitment threshold for most motor units (full recruitment assessed in a nonfatigued state). In agreement with previous investigations, generation of large torques about a single joint was accompanied by increased force tremor and muscle activity in the limb performing the task (Allum et al. 1978; Löscher et al. 1994, 1996; Shinohara et al. 2003; Zijdewind et al. 2006; Zijdewind and Kernell 2001). Also consistent with previous work, it appears that strong isometric elbow flexion cannot be performed without increasing muscle activity in the contralateral homologous muscle(s) (Zijdewind et al. 2006). Brachioradialis and biceps activity increased from baseline levels in both limbs during the maximal contraction, which was accompanied by clear increases in the amplitude of forearm tremor for both limbs. Given that the LOA for brachioradialis and biceps was high, and the contraction likely exceeded the recruitment threshold for most motor units (full recruitment occurs at ~80% MVC for most nonhand muscles; Duchateau et al. 2006), considerable cortical drive was directed toward the target motor neuron pool. Strong cortical activity associated with voluntary contractions is known to alter excitability of motor pathways originating in the contralateral hemisphere (Hess et al. 1987; Stedman et al. 1998; Zwarts 1992), and this irradiation may have played a role in directly activating the non-target limb.

Interestingly, bilateral increases in tremor and muscle activity during the brief unilateral contractions were not accompanied by changes in between-limb coupling. That is, the increased tremor observed in the contralateral limb was generated as an indirect consequence of increased oscillatory neural drive to the active limb. One possible explanation is that the considerable excitatory drive to the contracting muscles caused residual activation of cortical motor areas for the nonactive limb (Liu et al. 2003; Post et al. 2009; Zijdewind et al. 2006). This residual activity may have led to increased muscle and tremor responses in the nonactive limb; however, the exact nature of the response was not dependent on the active limb. In other words, activity in the nonactive limb may be due to a “spillover” effect rather than directly coupled neural output to...
both arms. This finding builds upon our knowledge that physiological tremor is relatively independent in each limb, and is believed to be generated by parallel oscillators (Llinas 1984, 1991; Llinas and Pare 1997; Marsden et al. 1969a). However, coupling between the output of neural pathways that facilitate between-limb tremor is only altered under considerably perturbed conditions, such as fatigue-inducing contractions (see next section).

While it is likely that bilateral responses to maximal-effort unilateral contraction were centrally mediated, the role of afferent input to the CNS should also be considered. It cannot be ruled out that larger-diameter afferents contributed to the observed bilateral response, because even under isometric contractions spindle discharge frequency increases with the intensity of muscle contraction (Vallbo 1974). Although Ia afferents play an integral role in tremor within a limb (Christakos et al. 2006; Hagbath and Young 1979), contralateral effects arising from Ia afferents are typically considered weak. Instead of directly influencing the contralateral limb, crossed effects are modulated indirectly via propriospinal pathways (McCrea 1986; Mezzarane et al. 2012). During the maximal contraction there may have been sufficient increases in intramuscular pressure to cause mechanical deformation, thus increasing the activity of group III afferents. Motor neuron excitability in the contracting limb can be regulated according to group III feedback (Bigland-Ritchie et al. 1986a); however, the effect of differing levels of feedback on motor neurons and tremor responses in the contralateral limb is largely unknown.

Unilateral Fatigue Differentially Affected Tremor for Each Limb

By comparing data from the first set of the fatigue task to data from the last set of the fatigue task, it was possible to determine how unilateral fatigue affected bilateral tremor and muscle activity. The principal finding in this experiment is that by the final set of the fatigue task tremor was decreased in the exercising limb and increased in the nonexercising limb. These fatigue-related changes occurred in parallel with brachioradialis activity (but not biceps activity; Fig. 5), indicating that fatigue-related changes for brachioradialis had the greatest influence in bilateral tremor regulation for the adopted experimental posture. To determine whether the alterations in tremor for the nonexercising limb were a consequence of movement artifact, data were also examined during the rest periods of the fatigue task. That is, we sought to reduce the possibility that enhanced tremor in the noncontracting limb was simply a consequence of generalized cocontraction, or “tensing up” the whole body, while trying to perform the repeated maximal contractions. Given that postural tremor remained elevated even when subjects were in the resting postural position, it appears that activity in the contralateral limb was due to the unilateral fatigue task and not a consequence of unintended mechanical coupling.

In contrast to the effects observed for brief maximal unilateral contraction, unilateral fatigue induced changes in between-limb coupling dynamics. The strength of between-limb correlation for biceps and brachioradialis EMG decreased from the beginning to the end of the fatigue task. This was accompanied by an increase in time lag between biceps EMG oscillations and a reduction in time lag between brachioradialis EMG oscillations. Once again, brachioradialis played a significant role in tremor dynamics for the adopted posture, as the reduced time lag for brachioradialis oscillation aligned with an increase in synchrony for bilateral tremor. Increased bilateral synchronization implies that inputs to each elbow flexor, and particularly the brachioradialis motor neuron pool, had a common central source. Increased common drive to both limbs may have been influenced by a combination of feedforward mechanisms and peripheral afference from the fatigued limb. However, there is a suggestion that afferent fibers have no direct effect on motor units in the contralateral limb (Arya et al. 1991; Harrison and Zytnicki 1984) and do not play a direct role in modulating coupling with the contralateral limb (Boonstra et al. 2008). Instead, afferents from the fatiguing muscle may have played a role in regulating excitatory drive to the fatiguing limb at the cortical level that modulated activity in neural pathways to the contralateral limb.

While this was the first study to use twitch interpolation to examine the effects of fatigue on tremor, it is difficult to determine how central and peripheral mechanisms of fatigue contributed to the tremor response. The contraction protocol used in this study caused similar reductions in LOA and RT for the elbow flexors, indicating that there was reduced capacity to activate the muscles in addition to failure of their contractile mechanisms (Bigland-Ritchie et al. 1983, 1986b). The mechanisms underlying reduced RT include impaired excitation-contraction coupling, metabolite accumulation, reduced substrate availability, and restricted blood flow, each of which may impact on within-limb tremor to some extent. Although these adaptations were most likely localized to the exercising muscle—particularly given the relatively small muscle mass engaged (Lewis et al. 1985)—there may be subtle systemic perturbations that mediate activity in the contralateral homologous muscles. For example, isometric fatiguing hand grip increases circulating catecholamines and muscle sympathetic nerve activity in nonexercising muscles (Gunnar Wallin et al. 1992; Mark et al. 1985; Seals and Enoka 1989), both of which can independently increase tremor (Ahrens 1990; Baker and Baker 2012; Koster et al. 1998; Marsden et al. 1967).

Despite the potential contributions of systemic perturbations or peripheral afference, it is evident that there was a central response to the fatigue task. The observed declines in LOA and EMG for the exercising limb indicate that voluntary drive to the target muscle was impaired. These declines in LOA and EMG are consistent with previous intermittent MVC studies, where it is estimated that a quarter of the loss of elbow flexion force is due to supraspinal fatigue (Taylor et al. 2000, 2006). Although supraspinal mechanisms were not directly measured in the present study, Post et al. (2009) showed that changes in twitch interpolation—similar to what was employed in the present study—closely reflect changes in activity of cortical motor areas (fMRI). Specifically, 126 s of maximal unilateral isometric finger abduction caused declines in voluntary drive to the target muscle, which were associated with increased activity in the contralateral primary motor cortex and secondary motor areas. Although the contraction task of Post et al. was different in modality and duration from the present study, it is of interest that reduced voluntary drive to the target muscle was associated with increased activity not only in the contralateral hemisphere but also in the ipsilateral hemisphere and nontarget homologous muscle. Therefore, a cortical mechanism may be responsible for the crossed effects seen with high-intensity
contractions (Dettmers et al. 2006; Post et al. 2009; van Duinen et al. 2008).

Maximal-effort unilateral voluntary contractions have complex and task-specific crossed effects. Through a series of observations made from neurostimulation and neuroimaging studies, the most influential site of contralateral transfer for voluntary and fatiguing contractions is at the level of the cortex. Hortobágyi et al. (2003) performed an elegant study that showed that moderate to strong voluntary contractions of the left wrist are associated with increased motor evoked potentials (MEPs), unchanged cervicomedullary MEPs (CMEPs), and decreased H-reflex excitability in homologous right limb muscle. The authors suggest that the observed between-limb interactions during the brief contractions could be attributed to changes in cortical excitability and reduced spindle input to the motor neuron pool. In a context that is more related to the fatigue task in the present study, fMRI has revealed that during repetitive submaximal hand grips (30% MVC, 2-s contraction, 1-s rest), activation progressively increases in the contralateral motor cortex to maintain force output, before reaching an upper activation limit and then declining (Liu et al. 2003). Despite declines in the contralateral motor cortex directly involved in the fatiguing task, activity in the ipsilateral cortex progressively increases over the duration of the task. While this cortical activation could represent a number of responses such as the added processing of fatigue-related sensory information (Pettier et al. 2005), facilitation of inhibitory pathways, or adjustments in descending drive to the target muscle (Hellwig et al. 2000; Raethjen et al. 2007), it may also represent increased drive to the nonexercised limb (Post et al. 2009).

**Conclusions**

Applying loads to a single limb increased tremor and muscle activity in the loaded limb but did not affect the unloaded limb, indicating that manipulating the inertial characteristics of a limb does not evoke bilateral tremor responses. In contrast, maximal-effort unilateral isometric contractions resulted in increased tremor and muscle activity in both the active limb and the nonactive limb without any changes in between-limb coupling. When unilateral fatigue was induced, different tremor profiles were observed in each limb. That is, fatigue altered coupling between limbs and generated a bilateral response such that tremor and brachioradialis EMG decreased for the fatigued limb and increased in the contralateral nonfatigued limb. Our results demonstrate that activity in the nonactive limb may be due to a “spillover” effect rather than directly coupled neural output to both arms and that between-limb coupling for tremor and muscle activity is only altered under considerably perturbed conditions, such as fatigue-inducing contractions.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**


**REFERENCES**


