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Short-Interval Cortical Inhibition and Intracortical Facilitation during Submaximal Voluntary Contractions Changes with Fatigue

Sandra K. Hunter
Marquette University, sandra.hunter@marquette.edu

Chris J. McNeil
University of British Columbia

Jane E. Butler
University of New South Wales

Simon C. Gandevia
University of New South Wales

Janet L. Taylor
University of New South Wales

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Sandra K. Hunter
Exercise Science Program, Department of Physical Therapy, Marquette University, Milwaukee, WI
Chris J. McNeil
School of Health and Exercise Sciences, University of British Columbia, Kelowna, Canada
Jane E. Butler
Neuroscience Research Australia, Sydney, Australia
School of Medical Sciences, The University of New South Wales, Sydney, Australia
Simon C. Gandevia
Neuroscience Research Australia, Sydney, Australia
Prince of Wales Clinical School, The University of New South Wales, Sydney, Australia

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Janet L. Taylor

Neuroscience Research Australia,
Sydney, Australia
School of Medical Sciences, The University of New South Wales,
Sydney, Australia

Abstract: This study determined whether short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) change during a sustained submaximal isometric contraction. On 2 days, 12 participants (6 men, 6 women) performed brief (7-s) elbow flexor contractions before and after a 10-min fatiguing contraction; all contractions were performed at the level of integrated electromyographic activity (EMG) which produced 25 % maximal unfatigued torque. During the brief 7-s and 10-min submaximal contractions, single (test) and paired (conditioning–test) transcranial magnetic stimuli were applied over the motor cortex (5 s apart) to elicit motor-evoked potentials (MEPs) in biceps brachii. SICI and ICF were elicited on separate days, with a conditioning–test interstimulus interval of 2.5 and 15 ms, respectively. On both days, integrated EMG remained constant while torque fell during the sustained contraction by ~51.5 % from control contractions, perceived effort increased threefold, and MVC declined by 21–22 %. For SICI, the conditioned MEP during control contractions (74.1 ± 2.5 % of unconditioned MEP) increased (less inhibition) during the sustained contraction (last 2.5 min: 86.0 ± 5.1 %; $P < 0.05$). It remained elevated in recovery contractions at 2 min (82.0 ± 3.8 %; $P < 0.05$) and returned toward control at 7-min recovery (76.3 ± 3.2 %). ICF during control contractions (conditioned MEP 129.7 ± 4.8 % of unconditioned MEP) decreased (less facilitation) during the sustained contraction (last 2.5 min: 107.6 ± 6.8 %; $P < 0.05$) and recovered to 122.8 ± 4.3 % during contractions after 2 min of recovery. Both intracortical inhibitory and facilitatory circuits become less excitable with fatigue when assessed during voluntary activity, but their different time courses of recovery suggest different mechanisms for the fatigue-related changes of SICI and ICF.
Keywords: Transcranial magnetic stimulation, Motor-evoked potentials, Muscle fatigue, Elbow flexor muscles, Cortical inhibition, Cortical excitation

Introduction

Failure within the central nervous system contributes to a loss of force during and after fatiguing exercise (Gandevia 2001). Some of this failure occurs at a supraspinal level (Gandevia et al. 1996; Taylor et al. 2006). However, it remains unclear whether reduced motor

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cortical excitability may contribute to fatigability of human muscles. Excitatory and inhibitory responses to transcranial magnetic stimulation (TMS) over the motor cortex are altered during and after fatiguing contractions, but changes depend on the fatiguing task and precise methodology, so that apparently contradictory changes are described. When TMS is delivered during a voluntary contraction, the motor-evoked potential (MEP) is followed by a period of silence in surface electromyographic activity (EMG) recorded at the muscle (Inghilleri et al. 1993). During fatiguing contractions, the MEP tends to increase (Taylor et al. 1996; Sacco et al. 1997; Yoon et al. 2012), which suggests increased cortical excitability. In contrast, there is also an increase in the silent period following TMS (Taylor et al. 1996; Hunter et al. 2008; McNeil et al. 2009) and an increase in the suppression of voluntary EMG by very low intensity subthreshold TMS (Seifert and Petersen 2010), suggesting that motor cortical inhibition grows with fatigue.

Intracortical inhibition is commonly assessed with a paired-pulse TMS paradigm (Kujirai et al. 1993). This inhibition, whereby subthreshold TMS activates intracortical inhibitory circuits and reduces the size of an MEP elicited 2–5 ms later, is called short-interval intracortical inhibition (SICI). There is good evidence that SICI is due to activation of γ-aminobutyric acid (GABA) inhibitory circuits ($GABA_A$) in the primary motor cortex (Ziemann et al. 1996, 2001; Hanajima et al. 1998; Di Lazzaro et al. 2000). When SICI is tested at rest after fatiguing exercise, inhibition is reduced (Maruyama et al. 2006; Vucic et al. 2011) or not altered (Tergau et al. 2000). The reduction in SICI *after* a contraction (Maruyama et al. 2006; Vucic et al. 2011) contrasts with the finding of increased suppression of EMG by very low intensity TMS *during* a single-limb fatiguing contraction (Seifert and Petersen 2010) or sustained cycling (Sidhu et al. 2013), although this suppression is also thought to be mediated by $GABA_A$ receptors. In the non-fatigued muscle, voluntary drive reduces the excitability of the cortical inhibitory circuits, as measured by SICI, in cortical areas that represent the active muscle (Ridding et al. 1995; Reynolds and Ashby 1999; Ortu et al. 2008). Fatigue may further decrease the excitability of these circuits during voluntary drive (Williams et al. 2014), although it is not known if this decrease in SICI is independent of the increased voluntary drive that occurs during a constant-force contraction. The progressive increase in voluntary drive during a submaximal constant-

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force contraction presumably occurs because the active muscle fibers become fatigued, and more motor units are recruited to maintain the required force. Consequently, EMG activity increases (Lippold et al. 1960; Fuglevand et al. 1993; Carpentier et al. 2001; Riley et al. 2008). In concert with the increase in EMG is an increase in the MEP normalized to the compound muscle action potential (*M* wave), which typically does not change during low force sustained contractions (Sacco et al. 1997; Yoon et al. 2012). To determine whether SICI is influenced by the increasing voluntary drive, this study controlled for EMG activity rather than force, so that the motoneuronal output remained constant while sustaining a submaximal contraction (McNeil et al. 2011a).

Paired-pulse TMS over the motor cortex will also facilitate MEPs when the subthreshold stimulus is 10–15 ms prior to the MEP (Kujirai et al. 1993). The mechanisms for this intracortical facilitation (ICF) are not clear but may involve activation of excitatory cortico-cortical pyramidal cells (Chen et al. 1998). Facilitatory effects at both cortical and motoneuronal levels, however, may contribute to ICF (Kujirai et al. 1993; Ni et al. 2007). Similar to SICI, ICF has been tested with the muscle at rest *after* fatiguing exercise and yielded conflicting results; i.e., it either did not change (Maruyama et al. 2006) or decreased (Tergau et al. 2000). *During* a fatiguing voluntary contraction, ICF was not altered (Williams et al. 2014); although, like SICI, ICF is reduced during voluntary contraction compared with rest in the absence of fatigue (Ridding et al. 1995; Hanajima et al. 2002). It is not known how ICF responds to fatigue if one eliminates the increase in voluntary drive that occurs when force is maintained by keeping the EMG constant.

To understand fatigue-related changes in inhibition and facilitation in the motor cortex during voluntary activity, we determined whether SICI and ICF were altered *during* a sustained submaximal isometric contraction with the elbow flexor muscles. However, when the force is kept constant during a sustained contraction, the EMG increases (Lippold et al. 1960; Fuglevand et al. 1993; Carpentier et al. 2001; Riley et al. 2008). Hence, we controlled the level of motoneuronal output during the fatiguing contraction by requiring each participant to sustain the contraction at a constant level of integrated EMG rather than a constant torque. Given the reduction

in both SICI and ICF between rest and unfatigued voluntary activity, we *hypothesized* that SICI and ICF would be reduced during a submaximal sustained contraction and in the recovery period which followed. We also determined whether alterations in SICI and ICF were associated with the magnitude of the reduction in voluntary torque or increase in effort.

Methods

Fourteen healthy participants (7 men and 7 women) volunteered to participate in experiments on two separate days: one experiment to assess SICI and the other to assess ICF. Three participants were excluded from at least one session because of insufficient SICI (<12 %) or highly variable ICF at the best stimulus intensity. Hence, 12 participants (6 men and 6 women, 36 ± 2.9 years, 22–55 years) performed each experiment and 11 performed both experiments. All participants were healthy with no known neurological or cardiovascular disease. Prior to data collection, each participant provided written informed consent. All of the experimental procedures were approved by the University of New South Wales Human Research Ethics Committee and conducted according to the Declaration of Helsinki at Neuroscience Research Australia, Sydney, Australia.

Experimental setup and recordings

Participants were seated upright in an adjustable chair with the dominant arm held firmly at the wrist (via a secure strap) in an isometric myograph. The shoulder and elbow were flexed at 90° with the forearm vertical and fully supinated. The myograph measured isometric elbow flexion torque using a linear strain gauge (Xtran, Melbourne, Australia: linear to 2 kN). EMG signals were recorded with surface electrodes (Ag–AgCl, 10 mm diameter) placed over the middle of the muscle belly and the tendon of biceps brachii. The electrode placed over the muscle belly was ~midway between the anterior edge of deltoid and the proximal elbow crease for biceps. EMG signals were amplified (100–300×) and band-pass filtered (16–1000 Hz) (CED1902; Cambridge Electronic Design, Cambridge, UK). Torque (1000 Hz) and EMG (2000 Hz) signals were sampled with a CED1401 computer interface and Spike2 software (CED Ltd, Cambridge, UK).

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EMG of the biceps was also rectified and integrated using a 100 ms time constant (Neurolog System NL124A module; Digitimer, Welwyn Garden City, UK) and displayed on an oscilloscope for participant feedback.

Brachial plexus stimulation

The brachial plexus was electrically stimulated to produce a maximal compound muscle action potential (maximal *M* wave: M_{max}) of the biceps brachii. A cathode was placed in the supraclavicular fossa, and an anode on the acromion. A constant-current stimulator (model DS7AH, Digitimer, Welwyn Garden City, Hertfordshire, UK) was used to deliver single stimuli (100 μs duration). The stimulation intensity ranged between 80 and 220 mA.

Transcranial Magnetic Stimulation. The motor cortex was stimulated using a circular coil (13.5 cm outside diameter) attached via a Bistim unit to two Magstim 200 stimulators (Magstim, Dyfed, UK). One stimulator delivered the conditioning stimulus, and the other delivered the test stimulus. The coil was positioned with its center over the vertex to elicit MEPs in the biceps brachii of the dominant arm.

Several patterns of stimulation were delivered during submaximal voluntary contractions: a single test stimulus (producing the *unconditioned MEP*) and paired stimuli, in which a conditioning stimulus preceded the test stimulus (producing the *conditioned MEP*). A conditioning–test interstimulus interval of 2.5 ms was used to elicit SICI and 15 ms to elicit ICF. These interstimulus intervals were chosen based on initial pilot experiments in some of the same subjects. For each participant, the intensities of stimulation for the conditioning and test stimuli were set so that SICI or ICF in control contractions was ~50 % of the maximal inhibition or facilitation (for more detail see below). This allowed SICI and ICF to increase or decrease in fatigue and recovery. The intensities were expressed relative to the active motor threshold (AMT) of the MEP. AMT was established each testing day during control contractions (isometric voluntary contraction at 25 % of the torque produced in a maximal unfatigued voluntary contraction, MVC). See experimental protocol section for details.

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Experimental protocol

For each experiment, the procedures involved isometric contractions with elbow flexor muscles of the dominant arm. The protocol for each study was similar with the exception that the intensity and relative timing of the conditioning and test stimuli differed to elicit either SICI or ICF (as outlined above). MEPs were evoked by paired stimuli or a single test stimulus during a 10-min fatiguing contraction maintained at a level of EMG that produced 25 % maximal torque from the fresh muscle. MEPs (conditioned and unconditioned) were also evoked during 10 brief (~7 s) isometric contractions before and 2 and 7 min after the 10-min fatiguing contraction. See Fig. 1.

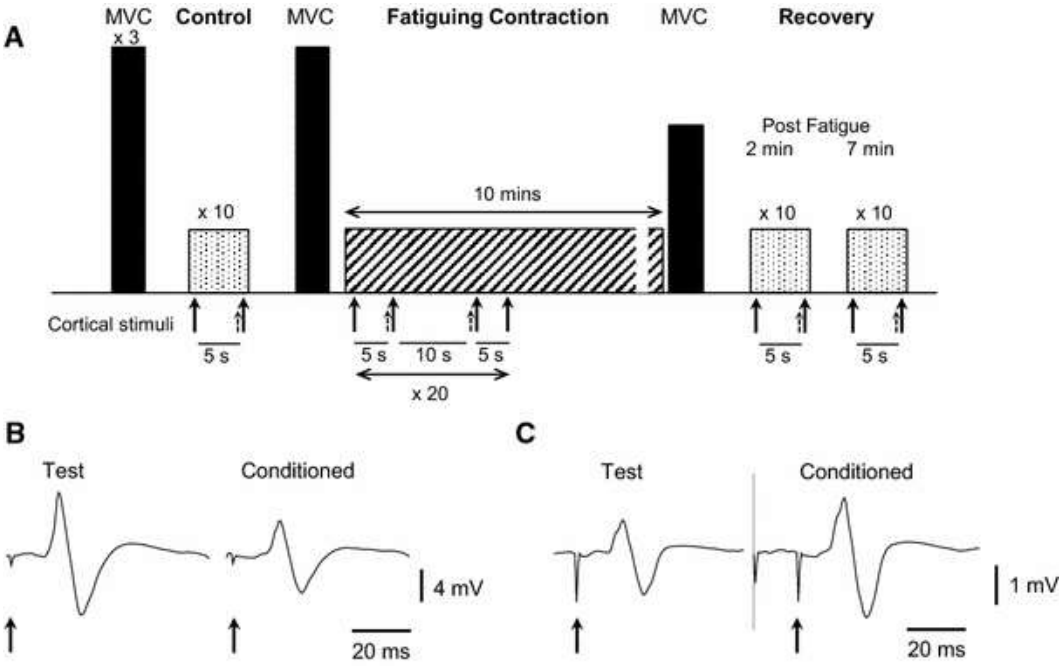

Fig. 1. Experimental protocol and raw data. **a** The experimental protocol is shown for both studies. Maximal voluntary contractions (MVCs) are shown in the *solid dark columns*, the 10-min fatiguing contraction is shown in the *striped bar* and the sets of 10 brief (~7 s) control contractions performed before (control) and at 2 and 7 min of recovery are shown in the *small spotted bars*. The brief control and recovery contractions as well as the 10-min fatiguing contraction were performed at the level of integrated EMG which produced 25 % maximal unfatigued torque. *Note* the figure is not to scale. Cortical test stimuli (conditioned and unconditioned) are indicated by the *solid arrows,* and the conditioning stimuli are indicated by the smaller *dashed arrows*. **b** Shown are the average of 10 test (unconditioned) motor-evoked potentials (MEPs) and 10 conditioned MEPs (2.5 ms interstimulus interval) elicited during control contractions of a single participant during the SICI protocol. **c** Shown are the average of 10 test (unconditioned) MEPs and 10 conditioned MEPs (15 ms interstimulus

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interval) elicited during control contractions of a single participant during the ICF protocol

The experimental procedures were as follows

1. M_{max} was established in relaxed biceps brachii by increasing the stimulation intensity incrementally for successive stimuli until the amplitude of the compound muscle action potential reached a plateau. Intensity of stimulation was increased by 20 %, and then a further three stimuli delivered. M_{max} was measured once at the start of the protocol.
2. *Maximal voluntary contractions* To establish peak torque, two or three MVCs of the elbow flexor muscles were performed with ~2 min rest between each contraction. Strong verbal encouragement and visual feedback of torque were provided during each maximal effort. With a target set from the MVC torque, a 5–10 s contraction was performed at 25 % maximal torque and the corresponding level of biceps-integrated EMG was identified and a target was set with a cursor on an oscilloscope. Participants used this EMG-based target on the oscilloscope for the remainder of the experiment. The EMG target is subsequently referred to as 25 % MVC.
3. *Active motor threshold* (*AMT*) was next established at 25 % MVC. AMT was taken as the minimum stimulator output required to yield visible MEPs (~50 μV) in 6 of 10 stimuli delivered during 5 voluntary contractions. Each contraction was ~7 s duration so that 2 stimuli were delivered 5 s apart during each contraction.
4. *Intensity for test stimulus and conditioning stimulus* Maximal levels of inhibition or facilitation were established, and the intensity of the stimuli adjusted to provide ~50 % of the maximal SICI or ICF so as to allow the inhibition or facilitation to increase or decrease in fatigue. For each participant, the test stimulus was initially set to 120 % of AMT and the conditioning stimulus to 90 % AMT and test and conditioned MEPs were evoked during sets of 5–10 contractions of ~7-s duration at 25 % MVC at 20-s intervals. The intensity of the conditioning stimulus (and test stimulus, if necessary) was then adjusted, and SICI or ICF retested to determine the maximal inhibition or facilitation. Next, the intensities which evoked ~50 % of the maximal SICI or ICF were established; these intensities were used for the remainder of the experiment. SICI was elicited with the conditioning stimulus at 78 ± 2 % of AMT and the test stimulus at 122 ± 1 % of AMT. In the second set of experiments, ICF was elicited with a conditioning stimulus at 81 ± 2 % AMT and test stimulus at 119 ± 1 % AMT.

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5. *Control contractions to elicit control SICI or ICF* Pre-fatigue (control) values for the unconditioned MEP and conditioned MEP were obtained during 10 contractions performed at 25 % MVC. Each contraction was ~7 s in duration with 20 s between the start of each contraction. Each participant increased biceps EMG to the target and received a single test stimulus to the cortex (unconditioned MEP) followed 5 s later by paired cortical stimuli (conditioned MEP). The order of test and paired stimuli was alternated with each subsequent contraction.
6. *A single MVC* was performed to establish that peak torque remained within 5 % of the initial level measured prior to the contractions performed during setup and for control measurements.
7. *Fatiguing submaximal contraction* The fatigue protocol was a sustained 10-min contraction during which biceps-integrated EMG was held at the level that initially produced 25 % of maximal torque. During the contraction, participants were provided with EMG feedback and were routinely reminded to maintain the EMG feedback signal as near as possible to the target cursor. The same stimulation sequence used during control contractions was delivered throughout the fatiguing contraction so that a single test stimulus and paired cortical stimuli were delivered 5 s apart followed by 10 s before another sequence of stimuli was given in the alternate order (paired stimuli followed by a test stimulus). Hence, 4 sets of stimuli were delivered each minute (i.e., a test and paired stimuli sequence) and 40 sets (or 80 MEPs) over the 10-min contraction. Participants rated their perceived effort on 1-to-10 modified Borg scale each minute during the fatiguing contraction (Borg 1998). Perceived effort was also obtained during control and recovery contractions in both sets of experiments.
8. *Recovery* One MVC was performed immediately after the 10-min fatiguing contraction. At 2 min and also 7 min after the fatiguing contraction, series of 10 contractions at 25 % MVC (biceps EMG target) were performed as per control contractions. That is, unconditioned MEP and conditioned MEP were elicited 5 s apart during each contraction which lasted ~7 s. Contractions were 20 s apart.

Data analysis

Signal software (v. 3.05; Cambridge Electronic Design) was used to determine all measures during off-line analysis. Mean torque and voluntary EMG were calculated over 100 ms in the interval 105–

5 ms prior to the test stimulus in the SICI experiments and 115–15 ms prior to the test stimulus in the ICF experiments. MVC torque was calculated as the peak value of the brief contractions. The areas of M_{max} and MEPs were measured between cursors marking the initial deflection from the baseline to the second crossing of the horizontal axis (Martin et al. 2006). SICI and ICF were calculated as the ratio (expressed as a percentage) between the areas of the conditioned and unconditioned MEPs (conditioned/unconditioned × 100). Control and recovery SICI and ICF values were calculated using the mean values of the conditioned and unconditioned responses obtained during each set of 10 brief contractions [control, 2-min recovery (Rec 2 min) and 7-min recovery (Rec 7 min)]. During the 10-min fatiguing contraction, SICI and ICF values were calculated using the mean values of the conditioned and unconditioned responses in groups of ten (1–10, 11–20, 21–30 and 31–40). Hence, for the 10-min fatiguing contraction, four SICI and ICF values (Fat 1–10, Fat 11–20, Fat 21–30 and Fat 31–40) were calculated for each participant.

Statistical analysis

Data are reported as means ± SEM in the text and figures. The significance level was considered $P < 0.05$. One-way repeated measures ANOVAs were used to compare variables across time for the SICI and ICF experiments, separately (SPSS version 21; SPSS Inc., Chicago, IL, USA). Comparisons included initial non-fatigued (control) MVCs, MVC torque before and after fatigue, torque during the submaximal contractions, RMS EMG amplitude, unconditioned MEP area of biceps, SICI ratio, ICF ratio and perceived effort. Five levels were compared for the effect of time (control, Fat 1–10, Fat 31–40, Rec 2 min and Rec 7 min), and pairwise comparisons were used to detect differences between the levels. The strength of an association between two variables is reported as the squared Pearson product-moment correlation coefficient (r^2). Variables correlated included the change in SICI or change in ICF with the absolute or percentage increase in perceived effort, loss of torque during the 10-min contraction, and the loss of MVC torque.

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Results

Study one: SICI

As designed, RMS of biceps EMG was similar between control, the fatigue and recovery contractions [time effect, $F(4,44) = 0.55$, $P = 0.70$] (see Fig. 2a). While the RMS EMG was held constant, perceived effort increased threefold from 2.4 ± 0.2 during control contractions to 7.0 ± 0.6 in the last (10th) minute of the fatiguing contraction ($P < 0.001$, Fig. 2a). In contrast, torque at 25 % RMS EMG decreased from 14.1 ± 1.1 Nm (23.5 ± 0.6 % MVC) during control contractions (prior to the test stimulus) to 11.5 ± 1.0 Nm in the first 2.5 min (Fat 1–10) and then to 6.8 ± 0.7 Nm in the last 2.5 min of the 10-min contraction (Fat 31–40) [$F(4,44) = 21.4$, $P < 0.001$; Fig. 2a]. This was a 51.0 ± 4.0 % decrease in torque between control and the last 2.5 min of the fatiguing contraction. By 7 min of recovery, torque had increased to 10.5 ± 0.9 Nm but this was still 26.0 ± 2.7 % less than control.

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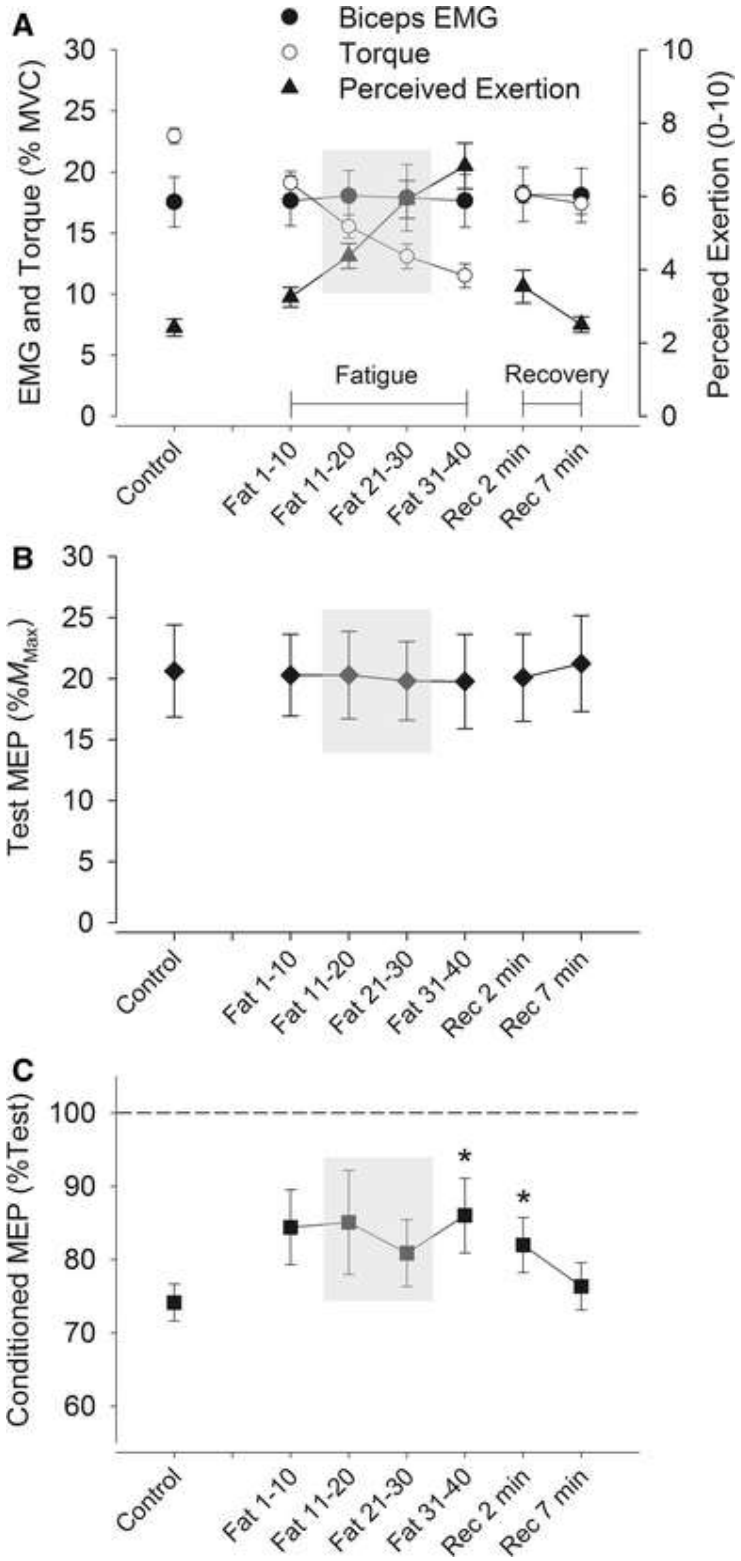

Fig. 2. Data from the short-interval cortical inhibition experiments. Each panel (**a**, **b**, **c**) shows the mean (±SEM) data during control contractions, during the 10-min

fatiguing contraction and recovery. Each data point is the mean of 10 data points for each participant (except perceived exertion) and then averaged for the 12 participants. **a** Shown on the left *y*-axis is integrated EMG activity of biceps brachii (*closed circles*) and the corresponding elbow flexor torque (*open circles*). On the right *y*-axis is the rating of perceived exertion (*triangles*). During the 10-min fatiguing contraction, EMG activity was constant ($P > 0.05$), torque decreased ($P < 0.05$), and perceived exertion increased ($P < 0.05$). **b** Test (unconditioned) MEP (% of M_{max}) remained constant throughout the experiment ($P > 0.05$). **c** SICI decreased (i.e., conditioned MEP became more similar to the unconditioned MEP) at the end the fatiguing contraction and at 2-min recovery but then returned to control values by 7-min recovery (*Asterisk* represents a difference from control at $P < 0.05$). The values in the *shaded area* (Fat 11–20, Fat 21–30) are included in the figure to show the response time course, but they were not included in the statistical analyses

MVC torque was similar in the initial contractions and in the MVC just prior to the fatiguing contraction (59.8 ± 4.1 vs. 59.0 ± 3.9 Nm). Just after the 10-min fatiguing contraction, MVC torque decreased to 46.7 ± 3.7 Nm which was a 20.6 ± 4.8 % reduction from control MVC ($P = 0.004$). The RMS EMG of the biceps brachii during the MVC immediately after the 10-min contraction was 92.0 ± 8.6 % of the control MVC ($P = 0.51$).

The *M* wave amplitude and area (M_{max}) at rest were 18.3 ± 2.0 mV and 0.114 ± 0.013 mVs^{-1}, respectively. The unconditioned MEP area (%M_{max}) of biceps brachii stayed constant across the control period, the fatiguing contraction and the recovery period [time effect, $F(4,44) = 3.5$, $P = 0.13$; Fig. 2b]. When the area of the conditioned biceps brachii MEP was expressed relative to the unconditioned MEP (SICI ratio), there was a main effect of time [$F(4,44) = 4.5$, $P = 0.004$] because the ratio increased. Pairwise comparisons showed an increase from control contractions (74.1 ± 2.5 %) to the end of the fatiguing contraction (last 2.5 min: 86.0 ± 5.1 %, $P = 0.005$) and at 2-min recovery (82.0 ± 3.8 %, $P = 0.008$). At 2-min recovery, there was 10.7 % less inhibition than control, but then SICI returned to control levels during the contractions at 7 min of recovery (76.3 ± 3.2 %, $P = 0.34$).

Study two: ICF

Similar to the SICI experiments, RMS EMG of biceps (25 % MVC) remained constant, perceived effort increased and torque decreased during the 10-min fatiguing contraction. Biceps RMS EMG was similar between the control, and fatiguing and recovery

contractions [time effect, $F(4,44) = 1.6$, $P = 0.27$; Fig. 3a]. Perceived effort increased threefold by the end of the fatiguing contraction (2.3 ± 0.2 in control contractions to 6.7 ± 0.6 in the 10th minute of the fatiguing contraction, $P < 0.001$) and then recovered to control levels during the 7 min of recovery contractions (2.4 ± 0.2; Fig. 3a). In contrast, target torque at 25 % RMS EMG decreased from 14.2 ± 1.1 Nm (23.6 ± 0.8 % MVC) during control contractions (prior to the test stimulus) to 11.2 ± 1.1 Nm in the first 2.5 min (Fat 1–10) and then to 6.8 ± 0.7 Nm in the last 2.5 min of the 10-min contraction (Fat 31–40) [time effect, $F(4,44) = 26.1$, $P < 0.001$; Fig. 3a]. Torque, therefore, decreased from control by 52.2 ± 3.5 % in the last 2.5 min of the fatiguing contraction. Target torque increased to 10.2 ± 0.8 Nm at 7-min recovery, but this was still 27.4 ± 2.1 % less than control.

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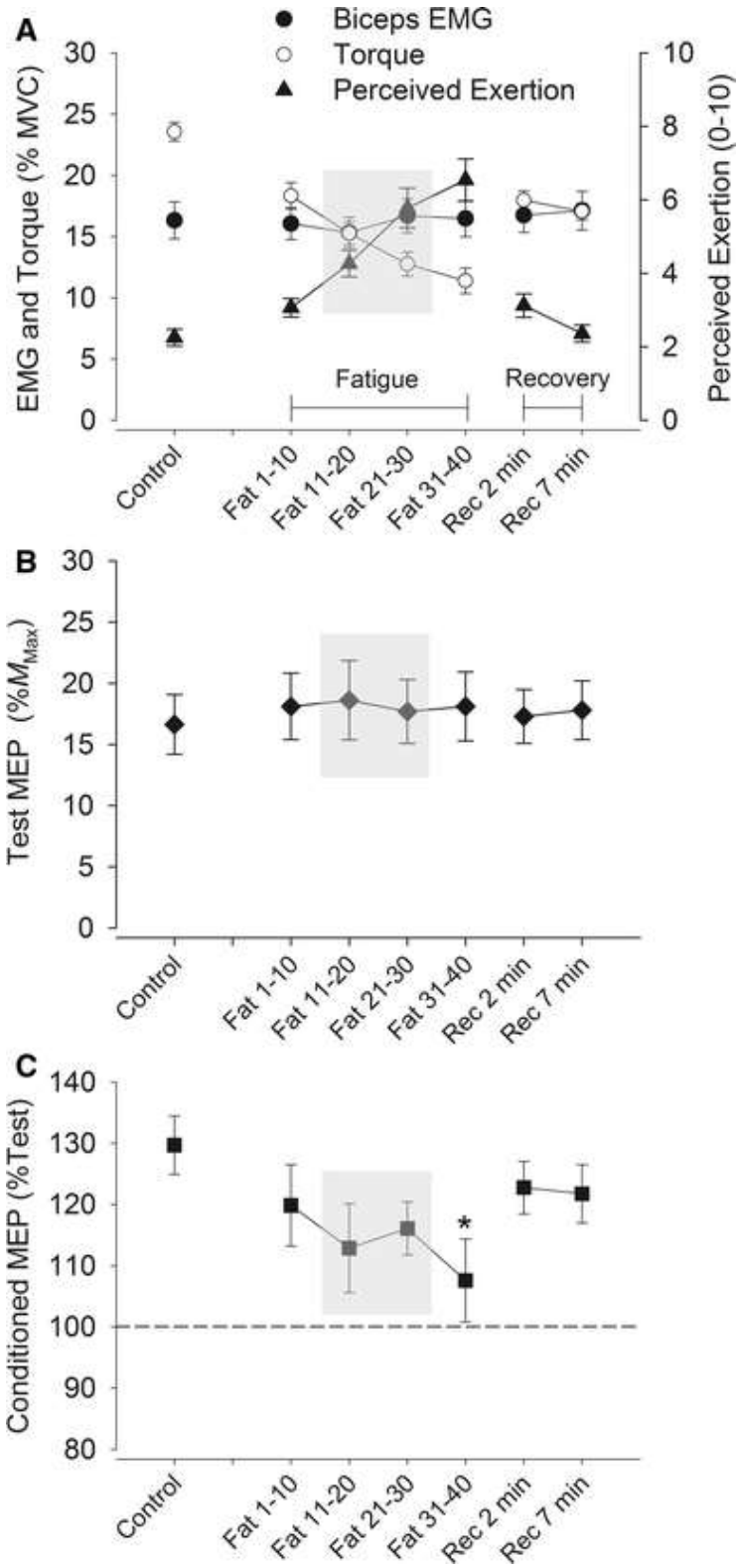

Fig. 3. Data from the intracortical facilitation experiments. Each panel (**a**, **b**, **c**) shows the mean (±SEM) data during control contractions (control), during the 10-min

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fatiguing contraction and recovery. Each data point is the mean of 10 data points for each participant (except perceived exertion) and then averaged for the 12 participants. **a** Shown on the left *y*-axis is integrated EMG activity of biceps brachii (*closed circles*) and the corresponding elbow flexor torque (*open circles*). On the right *y*-axis is the rating of perceived exertion. During the 10-min fatiguing contraction, EMG activity was constant ($P > 0.05$), torque decreased ($P < 0.05$), and perceived exertion increased ($P < 0.05$). **b** Test (unconditioned) MEP (% of M_{max}) is shown and remained constant throughout the experiment ($P > 0.05$). **c** ICF decreased (i.e., conditioned MEP became more similar to the unconditioned MEP) by the end of the 10-min contraction ($P < 0.05$) and then returned to control levels by 2-min recovery (*Asterisk* represents a difference from control at $P < 0.05$). The values in the shaded area (Fat 11–20, Fat 21–30) are included in the figure to show the response time course, but they were not included in the statistical analyses

MVC torque was similar in initial measurements before the control contractions compared with just prior to the fatiguing contraction (60.2 ± 4.3 vs. 59.3 ± 4.1 Nm). MVC decreased at the end of the 10-min fatiguing contraction to 46.4 ± 3.9 Nm which is a 22.2 ± 3.7 % reduction from control ($P < 0.001$). The RMS EMG of the biceps brachii during the MVC immediately after the 10-min contraction was 96.5 ± 7.9 % of the control MVC ($P = 0.85$).

The *M* wave amplitude and area (M_{max}) at rest were 18.3 ± 2.3 mV and 0.111 ± 0.016 mVs^{-1}, respectively. During the study, the unconditioned MEP area (%M_{max}) stayed constant in the control contractions, the fatiguing contraction and recovery contractions [time effect, $F(4,44) = 0.47$, $P = 0.76$; Fig. 3b]. The area of the conditioned MEP (expressed relative to the unconditioned MEP, i.e., ICF ratio) differed with time [time effect, $F(4,44) = 2.66$, $P = 0.045$]. Pairwise comparisons indicated that ICF decreased between control values and those at the end of the fatiguing contraction (Fat 31–40) (129.7 ± 4.8 vs. 107.6 ± 6.8 %, $P = 0.004$; Fig. 3c). Hence, there was 17.0 % less intracortical facilitation at the end of the fatiguing contraction compared with control. During recovery contractions, ICF values increased closer to control levels so that pairwise comparisons showed no difference between control and recovery at 2 min ($P = 0.31$) or 7 min ($P = 0.13$).

Correlations: torque, effort, SICI and ICF

Initial MVC was positively associated with the final perceived effort (at 10 min) of the sustained contraction (both sessions were included) ($n = 24$, $r = 0.63$, $r^2 = 0.39$, $P = 0.001$; Fig. 4a).

Furthermore, the greater the final perceived effort the larger the drop in MVC torque (% of initial MVC) that was assessed immediately after the 10-min contraction (n = 24, r = −0.58, r^2 = 0.34, P = 0.003, Fig. 4b). Accordingly, the loss in torque during the 10-min contraction sustained at 25 % initial EMG was correlated with the increase in perceived effort for both sessions combined (n = 24, r = 0.44, r^2 = 0.19, P = 0.034). Thus, those participants who had greater loss of absolute torque also had greater increases in perceived effort. All correlations for the SICI and ICF experiments considered separately (n = 12) were not significant, including the change in SICI or change in ICF with the absolute or percentage increase in perceived effort, loss of torque during the 10-min contraction, the loss of MVC torque.

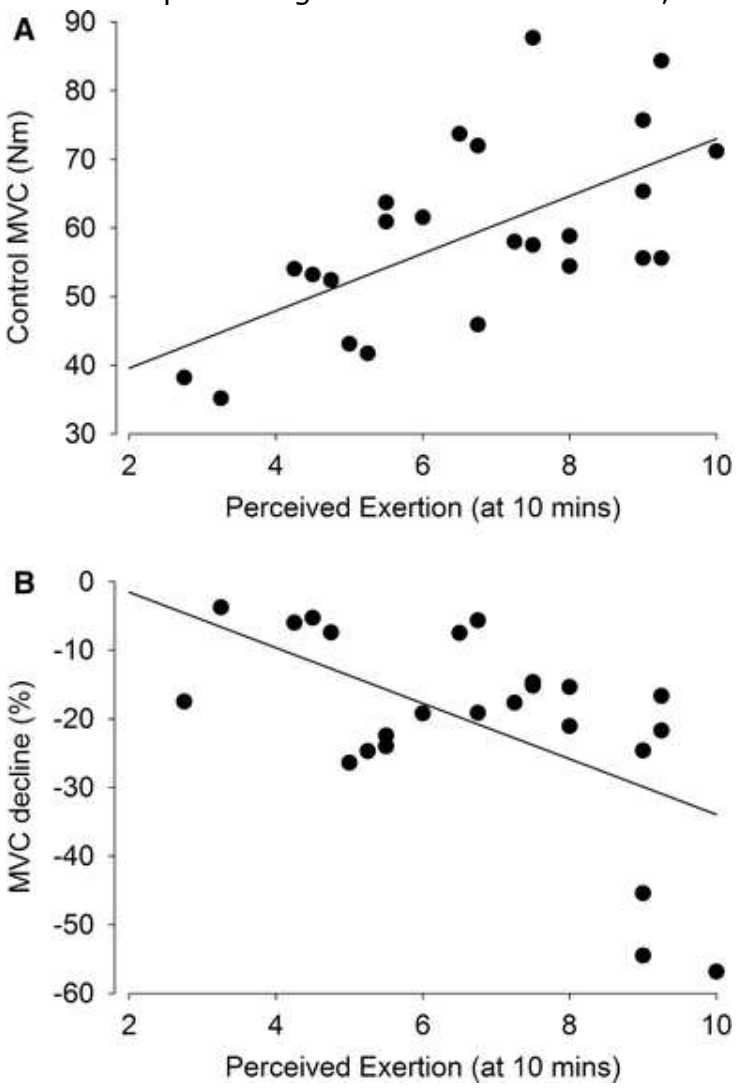

Fig. 4. a Associations between MVC torque and perceived exertion. Shown is a positive association between the control maximal voluntary contraction (MVC) torque

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(absolute strength) and the perceived exertion at the end of the 10-min fatiguing contraction (r = 0.63, r^2 = 0.39, P = 0.001). **b** Shown is a negative association between the reduction in MVC torque and the perceived exertion at the end of the 10-min fatiguing contraction (r = −0.58, r^2 = 0.34, P = 0.003). Data from both experiments (SICI and ICF) are included (n = 24) in each panel **a** and **b**

For those participants who completed both experiments (n = 11), the associations between SICI and ICF were not significant for either the relative changes from control to the end of 10-min contraction (r = −0.56, r^2 = 0.32, P = 0.07) or the absolute changes in SICI and ICF (r = −0.46, r^2 = 0.21, P = 0.15).

Discussion

This study determined whether SICI and ICF change during and in recovery from a sustained submaximal isometric contraction when EMG rather than force was held stable during voluntary contractions. The novel findings of this study are that (1) both SICI and ICF were detected when evaluated *during* a submaximal contraction performed with the elbow flexor muscles, (2) both SICI and ICF declined (conditioned MEP became more similar in size to unconditioned MEP) during the sustained fatiguing contraction, and (3) SICI took longer to recover than ICF during the recovery contractions, although both recovered to control levels by 7 min after the sustained fatiguing contraction. These data suggest that intracortical inhibitory and facilitatory circuits both become less excitable during submaximal sustained fatiguing voluntary activity.

Important methodological aspects of this study were that: (1) we tested SICI and ICF at submaximal levels rather than maximal levels to avoid any potential ceiling effect (e.g., Benwell et al. 2006) and allow the levels of inhibition or facilitation to vary with fatigue; (2) by requiring participants to maintain a constant EMG level, we attempted to control motoneuron activity and excitability as fatigue developed, and so minimize any potential changes in the amplitude of the unconditioned (test) MEP (e.g., Benwell et al. 2006; Maruyama et al. 2006; Takahashi et al. 2009). During a sustained fatiguing contraction held at a constant torque, the active muscle fibers progressively fatigue. Thus, the recruitment of additional motor units is required to sustain the required torque and is seen as an increase in EMG (e.g., Lippold et al. 1960; Fuglevand et al. 1993; Carpentier et al.

2001; Riley et al. 2008). In the current protocol, in which the level of biceps brachii EMG stayed steady, we showed that in both protocols the unconditioned MEP remained stable before, during and after the fatiguing contraction, but SICI and ICF decreased. The MEP will usually increase during a sustained fatiguing contraction when the force is held constant (Sacco et al. 1997; Yoon et al. 2012). While changes in neuromuscular propagation can sometimes contribute to such increases (Fuglevand et al. 1993; Taylor et al. 1999), changes in the muscle compound action potential (*M* wave) are typically minimal during sustained submaximal contraction protocols (Yoon et al. 2012). We did not measure M_{max} during contractions in these protocols of the current study, but any change is likely to be small (McNeil et al. 2011a). Regardless, SICI and ICF involve a ratio of the unconditioned and conditioned MEPs that were elicited at similar times during contraction, so that any effects of altered neuromuscular propagation will be canceled in this ratio and not affect measurements of SICI and ICF.

The 10-min constant EMG contraction induced substantial fatigue that was similar across both protocols. The submaximal torque was reduced by ~51–52 % for both protocols which, when considered as absolute force, was equivalent to ~12–13 % of the control MVC [(control torque − Fat 31–40 torque)/control MVC torque × 100]. The MVC performed immediately upon completion of the 10-min contraction, however, was reduced by 22–23 %. This decline in MVC torque was larger than expected or predicted from the loss in submaximal torque, suggesting that central mechanisms contributed to the fatigability. The RMS EMG of the biceps during the MVC showed no significant decline from the control MVC to the MVC performed after the 10-min contraction, and we did not quantify voluntary activation and central fatigue directly with the interpolated twitch technique during the MVC (Gandevia 2001). However, the participants' fall in MVC was positively correlated with perceived effort near the end of the submaximal contraction; i.e., the greater the effort to maintain the submaximal contraction, the greater the fall in MVC. Similar to previous studies (Smith et al. 2007; McNeil et al. 2011a), there was a large mismatch between perceived effort and actual capacity to generate torque at the end of the submaximal contraction. Perceived effort increased threefold in both sets of experiments despite constant EMG activity and a falling torque. Across participants, those who

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reported higher final perceived effort were stronger and hence had higher target torques. This relationship is consistent with an influence of fatigue-sensitive small-diameter afferents on perceived effort, as higher muscle forces lead to higher intramuscular pressure, poorer perfusion, and increased concentrations of metabolites (Kennedy et al. 2013; Kennedy et al. 2014; Kennedy et al. 2015). However, this is unlikely to be the only factor underlying increasing effort. Profound decreases in motoneuron responsiveness occur during both submaximal and maximal isometric contractions (McNeil et al. 2009, 2011a, b) so that an increased level of descending drive is likely required to keep a constant motoneuronal output and thus keep EMG stable. Yet, there was no change in the size of the unconditioned MEP in either experiment and we found no association across subjects between the change in SICI or ICF with the increase in effort or reduction in maximal voluntary torque or the submaximal torque decline during the 10-min contraction.

Fatigue reduces SICI during voluntary activity

The decrease in SICI we observed during sustained fatiguing voluntary activity of the elbow flexor muscles is consistent with the reduction in intracortical inhibition (SICI) when tested after fatiguing exercise while the muscle was at rest (Benwell et al. 2006; Maruyama et al. 2006; Takahashi et al. 2009; Vucic et al. 2011), and the recent report of decreasing inhibition during sustained submaximal contractions with a constant target force and hence, increasing EMG (Williams et al. 2014). Voluntary activity that is not fatiguing lessens SICI (Ridding et al. 1995; Fisher et al. 2002; Ortu et al. 2008), but here SICI decreased from control contractions to the end of the fatiguing contraction with a constant EMG (Fig. 2 shows an increase in values toward the unconditioned MEP, indicating less inhibition). The reduction in SICI was still present during contractions that began at 2 min of recovery but was restored to control levels 7 min after exercise. Similarly, in another study, SICI measured at rest after a 2-min intermittent fatiguing contraction (50 % MVC) was reduced at 5-min recovery but fully recovered at 10 min post-exercise (Maruyama et al. 2006). SICI therefore appears to be altered for several minutes after a fatiguing contraction.

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SICI reflects the suppression of indirect waves (*I*-waves), particularly the later *I*-waves (e.g., I_3), that follow the short latency direct wave (*D* wave) in the MEP (Di Lazzaro et al. 1998; Fisher et al. 2002; Reis et al. 2008). It is synaptic in origin and regulated by activation of inhibitory circuits ($GABA_A$) in the primary motor cortex (Ziemann et al. 1996, 2001; Hanajima et al. 1998; Di Lazzaro et al. 2000). A less inhibited motor cortex may represent compensatory effects to ensure adequate cortical excitation in response to the large fatigue-induced reductions in spinal motoneuron responsiveness (McNeil et al. 2011a). That is, while our constant-EMG contraction controlled motoneuronal output, cortical output to the motoneurons may have increased as if for a stronger voluntary contraction, although we found no association between perceived effort and the change in SICI. Alternatively, the loss of SICI could also be due to the superimposition of short intracortical facilitation [SICF, elicited with conditioning stimuli ~1–4 ms prior to the test stimuli (Ziemann et al. 1998)]. These excitatory circuits were proposed to decrease SICI during non-fatiguing contractions of the hand ≥25 % MVC when the conditioning stimulus was ≥80 % AMT (Ortu et al. 2008). Thus, the level of SICI measured in the paired-pulse paradigm could represent the balance between inhibitory and excitatory cortical interneurons. We tested SICI in these ranges of contraction and condition stimulus intensity. Whether SICF had an interaction with SICI which acted to decrease SICI over the course of the fatiguing contraction is not known.

The reduction in SICI remains paradoxical with respect to reported increases in TMS-evoked inhibition of voluntary EMG. In particular, intracortical inhibition following very low intensity TMS increased during sustained exercise (Seifert and Petersen 2010). The implication of the contrasting findings is that intracortical inhibition, mediated by $GABA_A$ receptors, is more effective at suppressing voluntary activity and less effective at suppressing evoked responses (MEPs) with fatigue, and our study confirms that this is not simply a difference between rest and activity. One possible explanation is that the two forms of brief intracortical inhibition do not share common circuitry, although that seems unlikely. However, the behavior of MEPs, which are produced by relatively synchronous input to the cortico spinal cells, is not always indicative of effects on voluntary motor output (e.g., McNeil et al. 2011c). Another possibility is that

EMG suppression found by Seifert and Petersen (2010) was achieved with lower stimulus intensities than used here and hence minimized simultaneous activation of excitatory circuits. While that appears not to be the case for elbow flexor muscle experiments (Seifert and Petersen 2010) (stimulus intensity of 0.85 active motor threshold), very low intensities were used by Sidhu et al. (2013) to inhibit leg muscles (mean 18.5 % stimulator output, 0.6 AMT) (Sidhu et al. 2013). Another consideration is that if the balance of effective excitation and inhibition elicited by the conditioning TMS is altered, then similar changes may occur in response to suprathreshold TMS, so that despite the constant size of the unconditioned MEP in our protocol, the way it is generated and its susceptibility to inhibition may be altered.

Fatigue reduces ICF during voluntary activity

ICF was reduced during a sustained fatiguing contraction with the elbow flexor muscles. These results are consistent with a decrease in ICF of the biceps brachii after bilateral fatiguing exercise when assessed at rest (Tergau et al. 2000). Others, however, showed no significant changes in ICF of the exercised limb after fatigue (Maruyama et al. 2006), although fatigue suppressed ICF in the homologous non-exercising muscle for up to 6 min after a fatiguing contraction of the first dorsal interosseous (FDI) (Baumer et al. 2002). In addition, Williams et al. (2014) found no change in ICF during a fatiguing submaximal contraction. However, facilitation prior to fatigue was minimal (conditioned MEP 104–107 % of unconditioned). Thus, while previous findings have implicated interhemispheric interactions, our results indicate that for a unilateral fatiguing isometric contraction, ICF is reduced for the exercising limb.

Voluntary activity that is not fatiguing lessens the magnitude of ICF compared to that evoked at rest (Ridding et al. 1995). The reduction in ICF in our results, however, is fatigue related because ICF continued to decrease during the fatiguing contraction relative to the initial control contractions (Fig. 3c). Recovery of ICF was rapid and occurred by the 2-min recovery contractions. This recovery occurred more rapidly than the recovery of SICI, suggesting different mechanisms are involved in the suppression of ICF and the loss of

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inhibition. It is still not fully understood what modulates ICF (Ni et al. 2007), although at baseline and during non-fatiguing voluntary activity, activation of cortico-cortical pyramidal cells and their axons are thought to be involved (Chen et al. 1998). In contrast, a recent model proposes that transmitter release from inhibitory interneurons may be depressed following their activation by the subthreshold conditioning TMS, thus decreasing the inhibitory component to a test stimulus evoked at ISIs greater than 5 ms (Rusu et al. 2014). This model implies that a decrease in SICI would lead to a decrease in ICF as occurred in the current study, although the different time course of recovery of SICI and ICF is not consistent with such a direct link.

In conclusion, we showed that both SICI and ICF were reduced during a fatiguing contraction with maintained motoneuronal output, but recovery took longer for SICI than ICF. In contrast, unconditioned MEP size was unchanged by the task. Furthermore, changes in excitability of the inhibitory and facilitatory intracortical circuits were not directly associated with the increase in perceived exertion, or the decrease in maximal voluntary force. This work reveals changes in the behavior of circuits within the motor cortex with fatigue, but it highlights that the overall impact on cortical output is difficult to discern.

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