Task-related changes in intracortical inhibition assessed with paired- and triple-pulse transcranial magnetic stimulation

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Throughout the central nervous system (CNS), inhibitory neurotransmission mediated through the activity of γ-aminobutyric acid (GABA) and its associated receptors represents a fundamental component of brain function. Important examples of this can be seen in the involvement of GABA in oscillatory activity and synaptic plasticity, processes thought to be important in learning and memory (Mann and Paulsen 2007; Paulsen and Moser 1998), as well as in facilitating sensory acuity via surround inhibition (Binns and Salt 1997; Kyriazi et al. 1996; Vučinić et al. 2006). Furthermore, alterations in GABAAergic function are thought to be associated with several pathological states, such as epilepsy (Treiman 2001) and schizophrenia (Benes and Berretta 2001; Lewis et al. 2005). Within human primary motor cortex, the activity of GABAAergic inhibitory circuits can be studied noninvasively using paired-pulse transcranial magnetic stimulation (TMS). When a subthreshold conditioning stimulus is applied at short interstimulus intervals (ISI; 1–5 ms) preceding a suprathreshold test stimulus, the amplitude of the test motor evoked potential (MEP) is reduced (Kujirai et al. 1993). This is referred to as short-interval intracortical inhibition (SICI) and is thought to be due to activation of postsynaptic GABAA receptors (Ziemann et al. 1996). Furthermore, when both conditioning and test stimuli are suprathreshold and separated by long ISIs (100–150 ms), a reduction of the test MEP amplitude is referred to as long-interval intracortical inhibition (LICI; Valls-Sole et al. 1992) and is thought to be due to activation of postsynaptic GABAA receptors (Werhahn et al. 1999). The magnitude of SICI and LICI may be altered in some movement disorders such as Parkinson’s disease, Huntington’s disease, and dystonia (Berrardelli et al. 2008), suggesting that these inhibitory circuits are important for basic motor control.

Voluntary activation of target muscles causes reductions in the magnitude of both SICI (Ridding et al. 1995) and LICI (Hammond and Vallence 2007), and this change in postsynaptic inhibition is thought to be functionally relevant (Sohn et al. 2002; Zoghi et al. 2003). In support of this, a recent study has shown that intracortical inhibition varies between tasks requiring different patterns of hand muscle activation, with greater reductions in both SICI and LICI occurring during synergistic as opposed to isolated muscle recruitment (Kouchtr-Devanne et al. 2012). Similar effects also have been reported for the cortical silent period (CSP), with greater reductions in CSP duration occurring during synergistic tasks (Tinazzi et al. 2003). This increased cortical disinhibition during synergistic tasks may facilitate the functional coactivation of the cortical representations for task-related muscles (Kouchtr-Devanne et al. 2012), resulting in improved task performance.

One factor that may influence these changes in SICI and LICI is a task-dependent modulation of presynaptic motor cortex inhibition, which can be assessed by quantifying the interaction between LICI and SICI (Ni et al. 2011b). This is examined in human motor cortex using a triple-pulse TMS protocol, where the conditioning and test stimuli used to assess SICI are preceded by a conditioning stimulus for LICI (Sanger et al. 2001). In a resting muscle, this pattern of stimulation results in a reduced inhibition of the test MEP relative to the inhibition observed during application of SICI in isolation (Sanger et al. 2001). Several lines of evidence suggest that this disinhibition of SICI circuitry occurs by GABAA receptor (LICI)-mediated presynaptic motor cortex inhibition (McDonnell et
finger, whereas in the other session they were required to activate the muscle by performing precision grip of the index finger and thumb. Because prolonged contractions were required to complete the multiple stimulation conditions needed for triple-pulse TMS (see below), assessing each active task on separate days reduced the likelihood of fatiguing the target muscle, which may have confounded measurements of intracortical inhibition (Benwell et al. 2006, 2007; Vucic et al. 2011). Within each experimental session, all TMS conditions (see below) were applied twice, once with the target muscle at rest and again with the target muscle active (either abduction or precision grip). Furthermore, paired-pulse TMS was always performed before triple-pulse TMS for all subjects, allowing the experimenter to monitor baseline levels of inhibition before applying triple-pulse TMS. During active state measurements, stimulation began after subjects had reached stable force application.

**Experimental Procedures**

**Maximal voluntary contraction.** At the beginning of each experiment, maximum voluntary contractions (MVC) were assessed for each subject. This was performed for both index finger abduction and during a precision grip using the index finger and thumb. During index finger abduction, the subject’s right hand was positioned with the palm facing downward and the index finger isolated from the middle, ring, and little fingers. When instructed, subjects abducted the lateral surface of the index finger against a force transducer (LC1205-K202; A&D Mercury, Thebarton SA, Australia) placed in-line with the distal interphalangeal joint. During precision grip, subjects opposed the index finger and thumb against a purpose built manipulandum that has been described previously (Opie and Semmler 2014). The procedure to assess the MVC was identical for both index finger abduction and precision grip: subjects were required to produce maximum force for 3 s in several repetitions, separated by 30 s rest, until the maximal force values of three trials were within a 10% margin. The largest force recorded during these trials was chosen as the subject’s MVC. To optimize force production, feedback was displayed on a computer monitor placed at eye level in front of the subject, and verbal encouragement was provided by the experimenter.

**Transcranial magnetic stimulation.** TMS was applied to the left primary motor cortex using a figure-of-eight coil (external wing diameter 9 cm) with three Magstim 200 magnetic stimulators connected via two Bistim units (Magstim, Dyfed, UK). Within this setup, two stimulators were connected via the first Bistim unit, whereas the third stimulator and the output from the first Bistim unit were connected via the second Bistim unit. The coil was then connected to the output of the second Bistim unit. This allowed application of up to three stimuli at very short intervals and different intensities through the same coil but was associated with a reduction in stimulus strength of ~15% (Sanger et al. 2001). During testing, the coil was held tangentially to the scalp at an angle of 45° to the sagittal plane, with the handle pointed backwards and laterally, producing a current flow in the brain with a posterior-to-anterior direction. The coil was positioned on the scalp over the location producing an optimum response in the relaxed FDI muscle. This location was marked on the scalp for reference and continually checked throughout the experiment. TMS was delivered at 0.2 Hz for all conditions.

Resting and Active motor thresholds (RMT and AMT, respectively) were obtained in FDI while the TMS coil was placed at the optimal location over primary motor cortex. RMT was defined as the minimum TMS intensity producing a response amplitude ≥50 μV in 3 of 5 trials in resting FDI muscle and was expressed relative to the maximum stimulator output (MSO). Active motor threshold (AMT) was defined as the minimum TMS intensity producing a response amplitude ≥300 μV in 3 of 5 trials while FDI was active at 5% MVC. Force feedback was provided via an oscilloscope placed at eye level in front of the subject, with a target force set on the oscilloscope that was adjusted to 5% of each subjects MVC.
Intracortical inhibition. The magnitude of intracortical inhibition was assessed using four experimental conditions (Table 1, conditions A–D). SICI was measured with a subthreshold conditioning stimulus set at 80% AMT and an ISI of 2 ms (condition B; Kujirai et al. 1993), whereas LICI was assessed using a suprathreshold conditioning stimulus set at 120% RMT and two ISIs of 100 and 150 ms (conditions C and D; Valls-Sole et al. 1992). For both SICI and LICI, the intensity of the test stimulus was set at the level producing an MEP with peak-to-peak amplitude of 1 mV when given alone (condition A; Stim1mV). Representative data from a single subject for each of these experimental conditions in resting FDI are shown in Fig. 1 (top 3 traces). Both paired-pulse TMS paradigms were applied in the same experimental block, allowing normalization of all paired-pulse responses to a common test alone state. Because 30 conditioned trials (10 SICI, 20 LICI) and 10 test-alone (control) trials were included within a block, and each block was repeated with the muscle at rest and during activation, a total of 80 trials were used to assess baseline levels of intracortical inhibition.

The effect of LICI on SICI was assessed using triple-pulse TMS (Table 1, conditions G–J). The conditioning stimulus used to activate LICI circuitry was set at 120% RMT and applied at two intervals of 100 ms (CS100, condition I) and 150 ms (CS150, condition J) in separate blocks. Within both blocks, the conditioning stimulus used to activate SICI circuitry was set at 80% AMT and applied using a 2-ms ISI (CS2). The effect of LICI on SICI (LICI-SICI interaction) was quantified by comparing the amplitude of the test MEP generated by application of all three stimuli (CS100/CS150, CS2, and a test stimulus) to the amplitude of the test MEP generated by application of the LICI conditioning stimulus and the test stimulus. The intensity of the test stimulus was adjusted to the level producing an MEP response of 1 mV when given alone (condition A; Stim1mV). Representative data from a single subject for each of these experimental conditions in the resting FDI are shown in Fig. 1 (bottom 2 traces). Because increasing test TMS intensity reduces the magnitude of SICI (Garry and Thomson 2009; Opie and Semmler 2014), the higher intensity Stim100 and Stim150 could account for changes in SICI observed during triple-pulse TMS. Therefore, additional measurements of SICI using Stim100 (SICIadj100) and Stim150 (SICIadj150) for the test stimulus were recorded as control states (conditions E and F, respectively). We refer to the test MEP generated during SICIadj100 and SICIadj150 as MEPadj100 and MEPadj150, respectively. Because 10 conditioned and 10 control trials were applied within 4 experimental blocks, and each block was repeated with the muscle at rest and during activation, a total of 160 trials were used to assess interactions between LICI and SICI.

Data Analysis

Data analysis was completed manually by visual inspection of offline EMG. Within the rest state, traces showing muscle activity >20 μV in peak-to-peak amplitude during the 150 ms preceding the MEP were excluded from analysis. MEP amplitudes from each trial were measured peak to peak and expressed in millivolts. Paired- and triple-pulse measurements of intracortical inhibition were quantified by expressing the amplitude of individual conditioned MEPs as a percentage of the average control MEP amplitude. Furthermore, to quantify the absolute change in SICI in response to adjusted intensity test stimuli (SICIadj100/SICIadj150) and triple-pulse stimulation (LICIadj/SICIadj), baseline SICI measurements were subtracted from adjusted intensity and triple-pulse SICI measurements for each task. For active trials, muscle activation was assessed by quantifying the root mean squared (rms) EMG amplitude (normalized to the maximum rmsEMG amplitude recorded during MVC) in the 100 ms leading up to application of CS150, CS100, or CS2 (depending on stimulation condition).

Statistical Analysis

RMT and AMT were compared between sessions using paired t-tests. Stim1mV, Stim100, and Stim150 in resting muscle were also compared between sessions using paired t-tests. Subject to no significant intersession differences, these data were pooled to investigate the effect of task (rest, abduction, and precision) on test stimulus intensity. This was assessed using a two-way repeated-measures analysis of variance (ANOVA) with factors of test stimulus condition (Stim1mV, Stim100, and Stim150) and task. Main effects and interactions were further investigated using one-way ANOVA with Fisher’s protected least significant difference (PLSD) post hoc test. Normalized EMG amplitude before TMS was assessed for SICI, LICI, and LICI-SICI interactions using individual two-way ANOVA and Fisher’s PLSD post hoc test.

Mixed-model analysis was used to investigate the effects of test MEP condition (MEP1mV, MEPadj100, MEPadj150, MEP100, and MEP150) and task on the amplitude of the test alone MEP. Individual mixed-model analyses were used to compare the effects of task on the magnitude of inhibition for SICI and LICI. The effect of LICI on SICI was also assessed using mixed-model analysis, with factors of SICI condition (baseline, SICIadj, and LICI-SICI) and task. This was investigated using separate models for each ISI. For all models, subject was included as a random effect, and significant interactions were further investigated using custom contrasts with Bonferroni correction. The absolute change in SICI relative to baseline within each stimulus condition was compared with zero (i.e., no change in magnitude of inhibition for SICI and LICI).

Table 1. TMS protocol

<table>
<thead>
<tr>
<th>Condition</th>
<th>CS150</th>
<th>CS100</th>
<th>CS2</th>
<th>Test Stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Test MEP1mV</td>
<td>120% RMT</td>
<td>80% AMT</td>
<td>Stim1mV</td>
<td></td>
</tr>
<tr>
<td>B SICI</td>
<td>120% RMT</td>
<td>80% AMT</td>
<td>Stim1mV</td>
<td></td>
</tr>
<tr>
<td>C LICIadj100</td>
<td>80% AMT</td>
<td>Stim1mV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D LICIadj150</td>
<td>80% AMT</td>
<td>Stim1mV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E MEPadj100</td>
<td>80% AMT</td>
<td>Stim1mV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F MEPadj150</td>
<td>80% AMT</td>
<td>Stim1mV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G SICIadj100</td>
<td>80% AMT</td>
<td>Stim1mV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H SICIadj150</td>
<td>80% AMT</td>
<td>Stim1mV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I Test MEPadj100</td>
<td>120% RMT</td>
<td>80% AMT</td>
<td>Stim100</td>
<td></td>
</tr>
<tr>
<td>J Test MEPadj150</td>
<td>120% RMT</td>
<td>80% AMT</td>
<td>Stim150</td>
<td></td>
</tr>
<tr>
<td>K LICIadj100</td>
<td>120% RMT</td>
<td>80% AMT</td>
<td>Stim100</td>
<td></td>
</tr>
<tr>
<td>L LICIadj150</td>
<td>120% RMT</td>
<td>80% AMT</td>
<td>Stim150</td>
<td></td>
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</tbody>
</table>

The transcranial magnetic stimulation (TMS) protocol included a conditioning stimulus applied 150 (CS150), 100 (CS100), or 2 ms (CS2) before the test stimulus in various conditions A–L. Test stimulus intensity was adjusted to the level producing a motor evoked potential (MEP) with peak-to-peak amplitude of 1 mV when given alone (Stim1mV) or when preceded by either CS100 (Stim100) or CS150 (Stim150). SICI, short-interval intracortical inhibition; LICI, long-interval intracortical inhibition; RMT, resting motor threshold; AMT active motor threshold. See text for definition of MEP amplitude conditions.
inhibition) using one-sample t-tests with Bonferroni correction. As a nonstandardized indication of effect size, estimated mean differences (EMD) and corresponding 95% confidence intervals (CI) are provided for post hoc comparisons. Significance was set at $P < 0.05$ for all comparisons, and data are shown as means [95% CI lower limit, upper limit], unless otherwise stated.

**RESULTS**

All subjects completed both experimental sessions in full and without adverse reaction. The subject cohort consisted of 7 females (21.4 [20.2, 22.6] yr) and 6 males (23.3 [18.5, 28.1] yr), and all subjects were right-hand dominant (average laterality quotient 0.92 [0.8, 1.0]). No differences were found between sessions for RMT (session 1: 61.8 [57.0, 66.5]% MSO, session 2: 60.5 [55.8, 65.1]% MSO, $P = 0.2$) or AMT (session 1: 47.0 [42.5, 51.5]% MSO, session 2: 47.6 [42.8, 52.4]% MSO, $P = 0.6$). MVC force was significantly greater during precision grip (51.0 [42.9, 59.2] N) than during index finger abduction (29.7 [23.3, 36.0] N, $P < 0.01$), whereas MVC EMG was significantly greater during index finger abduction (0.95 [0.8, 1.1] mV) than during precision grip (0.60 [0.4, 0.8], $P < 0.01$).

**Test MEP Characteristics**

The amplitude of the test alone MEP in each test stimulus condition is reported in Table 2. Analysis of these data revealed significant main effects of test MEP condition ($F_{4,1857} = 555.6, P < 0.01$) and task ($F_{2,1109} = 113.8, P < 0.01$), as well
MEPadj100 and MEPadj150 were significantly larger during in- as a significant interaction between factors ($F_{4,1848} = 113.3, P < 0.01$). As expected, these effects were driven by MEPadj100 and MEPadj150 being significantly larger than all other conditions (all $P$ values $<0.01$). Furthermore, compared with rest, both MEPadj100 and MEPadj150 were significantly larger during index finger abduction and precision grip (all $P$ values $<0.01$), but there was no difference in amplitude between abduction and precision grip for either variable. No significant differences in the amplitude of the adjusted test MEPs (MEP1mV, MEP100, and MEP150) were found between stimulus conditions or tasks (all $P$ values $>0.05$), suggesting that these were well matched to each other (Table 2). Test stimulus intensities for each test stimulus condition are shown in Table 2. Significant main effects of test stimulus condition ($F_{2,49} = 96.7, P < 0.01$) and task ($F_{2,49} = 23.1, P < 0.01$) were found, and there was a significant interaction between factors ($F_{4,98} = 15.4, P < 0.01$). Post hoc testing showed, for all conditions, that test TMS intensities in resting muscle were larger than during either abduction or precision grip (all $P$ values $<0.02$), but there was no difference in intensities between abduction and precision grip (all $P$ values $>0.3$). Furthermore, in resting muscle, Stim100 and Stim150 were both larger than Stim1mV (all $P$ values $<0.02$), whereas during both abduction and precision grip, Stim100 was larger than the other two states (all $P$ values $<0.002$), but there was no difference between Stim1mV and Stim150 (all $P$ values $>0.3$).

**Intracortical Inhibition**

Representative data from a single subject in resting FDI are shown in Fig. 1. For this subject, RMT was 69% MSO, AMT was 53% MSO, and MEP-Stim1mV was 80% MSO, whereas both MEP-Stim100 and MEP-Stim150 were 87% MSO. Baseline SICI for this subject was 60%, whereas baseline LICI was 50 and 26% for 100 and 150 ms ISI, respectively. During triple-pulse TMS, this subject demonstrated reduced SICI in the presence of LICI, with SICI of 114% observed when preceded by LICI at 100 ms, whereas SICI of 95% was observed when preceded by LICI at 150 ms.

**Short-interval intracortical inhibition.** The magnitude of baseline SICI for the three task conditions is shown in Fig. 2. These data show that the magnitude of SICI varied between tasks ($F_{2,158} = 142.9, P < 0.01$), with inhibition being significantly reduced (reflected by larger values) during both index finger abduction (EMD: 51.9%, 95% CI [41.1, 62.7], $P < 0.01$) and precision grip (EMD: 76.5%, 95% CI [63.9, 89.2], $P < 0.01$) compared with measurements in resting muscle (Fig. 2). Furthermore, measurements during precision grip were also significantly reduced relative to those recorded during index finger abduction (EMD: 24.6%, 95% CI [10.2, 39.1], $P < 0.01$). Normalized prestimulus rmsEMG amplitude during SICI measurements was significantly greater during precision grip than during index finger abduction ($P < 0.01$, Table 3). To address whether this increased muscle activation influenced SICI during precision grip, we reanalyzed a subset of 10 subjects that showed similar levels of muscle activation between abduction and precision grip. This subpopulation had average normalized EMG amplitudes of 11.0 [7.5, 14.5]% MVC EMG for abduction and 13.7 [10.6, 16.8]% MVC EMG for precision grip ($P = 0.2$). Reanalysis of the SICI data in this subpopulation showed results similar to those for the original sample, with SICI of 95 [82.4, 107.6]% during index finger abduction and 131 [113.7, 148.9]% during precision grip ($P < 0.01$).

**Long-interval intracortical inhibition.** Task- and timing-dependent variations in the magnitude of LICI are shown in Fig. 3. Main effects of task failed to reach significance ($F_{2,189} = 2.4, P = 0.1$), whereas the magnitude of inhibition varied between ISIs ($F_{1,240} = 90.7, P < 0.01$) and there was a significant interaction between factors ($F_{2,189} = 67.5, P < 0.01$). For measurements using a 100-ms ISI, LICI was significantly increased during both index finger abduction (EMD: 40.7%, 95% CI [30.1, 51.3], $P < 0.01$) and precision grip (EMD: 39.1%, 95% CI [28.4, 49.8], $P < 0.01$) compared with resting muscle. However, comparisons between abduction and precision grip showed that LICI100 was not differentially affected by the type of task performed ($P = 0.1$). In contrast, for

### Table 2. Test MEP characteristics

<table>
<thead>
<tr>
<th></th>
<th>MEP1mV (condition A)</th>
<th>MEPadj100 (condition B)</th>
<th>MEPadj150 (condition C)</th>
<th>MEP100 (condition D)</th>
<th>MEP150 (condition D)</th>
<th>Stim1mV</th>
<th>Stim100</th>
<th>Stim150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>1.1 [0.8, 1.3]</td>
<td>2.1 [1.8, 2.3]</td>
<td>2.4 [2.1, 2.6]</td>
<td>1.1 [0.9, 1.3]</td>
<td>1.1 [0.9, 1.3]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abduction</td>
<td>1.2 [0.9, 1.5]</td>
<td>7.2 [6.9, 7.5]</td>
<td>3.2 [2.8, 3.5]</td>
<td>1.2 [0.8, 1.5]</td>
<td>1.3 [0.9, 1.6]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precision</td>
<td>1.1 [0.8, 1.4]</td>
<td>7.3 [6.9, 7.6]</td>
<td>3.1 [2.8, 3.4]</td>
<td>1.1 [0.7, 1.4]</td>
<td>1.4 [1.1, 1.7]</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Values are means [95% confidence interval (CI) lower limit, upper limit]. *$P < 0.05$ compared with rest. ‡$P < 0.05$ compared with Stim1mV.
measurements using a 150-ms ISI, LICI was significantly reduced in response to index finger abduction (EMD: 36.7%, 95% CI [15.6, 56.9], P < 0.01) and precision grip (EMD: 58.1%, 95% CI [37.2, 79.0], P < 0.01) compared with resting muscle, although no differences in this effect were found between tasks (P = 0.2). Timing-related comparisons within each task condition demonstrated that, relative to LICI150, LICI100 was significantly reduced in resting muscle (EMD: 17.6%, 95% CI [8.3, 26.8], P < 0.01), whereas it was significantly increased during both abduction (EMD: 59.4%, 95% CI [42.9, 75.9], P < 0.01) and precision grip (EMD: 79.6%, 95% CI [62.9, 96.4], P < 0.01). Normalized prestimulus rmsEMG amplitude during LICI measurements was significantly affected by both task and ISI, with ~6% greater EMG amplitude during precision grip than during index finger abduction (P < 0.01) and 1% greater EMG amplitude at 100 ms compared with 150 ms (P < 0.01). The interaction between these factors failed to reach significance (P = 0.1) (Table 3).

SICI in the presence of LICI. Figure 4A shows the effect of LICI on SICI at an ISI of 100 ms. Analysis of these data showed significant influences of both stimulation state (F2,298 = 16.3, P < 0.01) and task (F2,317 = 51.0, P < 0.01), and a significant interaction between factors (F4,426 = 26.9, P < 0.01). With the muscle relaxed, the magnitude of inhibition was reduced during SICIadj100 (i.e., when SICI was reas-
sezsed using the increased test TMS intensity required for triple-pulse TMS) relative to baseline (EMD: 21.7%, 95% CI [13.0, 30.5], P < 0.01). During triple-pulse TMS, SICI at rest was reduced relative to both baseline (EMD: 63.0%, 95% CI [52.2, 73.8], P < 0.01) and SICIadj100 (EMD: 41.3%, 95% CI [29.9, 52.6], P < 0.01). During index finger abduction, the magnitude of inhibition did not vary between stimulation states (P values ranged from 0.06 to 0.9). However, during precision grip, SICIadj100 demonstrated increased inhibition relative to baseline (EMD: 29.6%, 95% CI [16.8, 42.3], P < 0.01), whereas the magnitude of inhibition produced by triple-pulse TMS was not different from either baseline (P = 0.1) or SICIadj100 (P = 0.4). Task-related comparisons within each stimulation state showed that SICIadj100 in resting muscle was significantly increased relative to measurements recorded dur-

### Table 3. Normalized prestimulus EMG for each TMS condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>Abduction</th>
<th>Precision</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline ICI</td>
<td>9.6 [6.5,12.3]</td>
<td>16.3 [12.5,20.1]</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>SICI</td>
<td>9.4 [6.4,12.4]</td>
<td>16.2 [12.2,19.8]</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>LICI100</td>
<td>9.1 [6.2,12.1]</td>
<td>15.2 [11.6,18.8]</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Test MEP</td>
<td>7.7 [5.7, 9.7]</td>
<td>15.7 [11.9,19.4]</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>SICIadj100</td>
<td>10.9 [7.9,14]</td>
<td>21.3 [14.5,28.2]</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Test MEP</td>
<td>9.3 [6.8,11.8]</td>
<td>22 [14.3,29.7]</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Values are means [95% CI lower limit, upper limit]. EMG, electromyography signal.
and index finger abduction during LICI\textsubscript{150}-SICI ($P < 0.004$; Fig. 4D). When triple-pulse TMS was applied using the 100-ms ISI, normalized prestimulus rmsEMG amplitude was $\sim 11\%$ greater during precision grip than during index finger abduction ($P < 0.01$). However, this difference was reduced to 7\% when the 150-ms ISI was used ($P = 0.04$) (Table 3).

**DISCUSSION**

The current study used paired- and triple-pulse TMS to investigate task-dependent variations in the modulation of intracortical inhibition. SICI, LICI, and the interaction between SICI and LICI were assessed while subjects were at rest or active in producing either isolated index finger abduction or synergistic precision grip of the index finger and thumb. At least three new findings can be drawn from the novel experimental approach used in this study. First, we found task-related variations in postsynaptic intracortical inhibition, with SICI (but not LICI) being particularly sensitive to the type of task performed (abduction vs. precision grip). Second, presynaptic motor cortex inhibition (assessed through LICI-SICI interactions) was modulated differently between abduction and

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**Fig. 4.** Task- and timing-dependent changes in LICI-SICI interactions. A and C: data show measurements of SICI when preceded by LICI\textsubscript{100} (A) or LICI\textsubscript{150} (C) using triple-pulse stimulation (LICI\textsubscript{100}-SICI, condition I; LICI\textsubscript{150}-SICI, condition J) during relaxation of FDI (solid bars), isolated index finger abduction (open bars), or precision grip of the index finger and thumb (shaded bars). A reassessment of baseline SICI with the increased intensity test stimulus used during triple-pulse stimulation is included as a control state (SICI\textsubscript{adj100}, condition E; SICI\textsubscript{adj150}, condition F). Dotted line represents no inhibition, with values below 100\% showing increased inhibition. B and D: the magnitude of change in SICI from baseline for the 100- (B) and 150-ms intervals is also quantified. Positively directed error bars show the upper limit of the 95\% CI; negatively directed error bars show the lower limit of the 95\% CI. #\(P < 0.004\) compared with baseline SICI. †\(P < 0.004\) compared with baseline SICI. *\(P < 0.05\).
cision grips, but this was evident for one ISI only (150 ms). Third, there was a divergent effect on LICI for different ISIs when the muscle was active, with LICI increasing at one ISI (100 ms) and decreasing at another (150 ms) for both tasks compared with rest.

Task-Related Variations in Postsynaptic Intracortical Inhibition (SICI and LICI)

During voluntary contraction, a reduction in GABAergic tone within primary motor cortex is thought to facilitate the activation of cortical areas innervating task-related muscles, subsequently allowing the generation of descending commands for movement (Matsumura et al. 1991, 1992). In humans, this reduction in inhibitory tone has been demonstrated for different GABA receptor subtypes by activity-dependent changes in SICI (Ridding et al. 1995), LICI, and the CSP (Hammond and Vallence 2007). In support of these observations, the current study observed reductions in both SICI and LICI in active muscle, although this effect for LICI depended on the ISI (see below).

Activity-dependent changes in GABAergic inhibition also have been suggested to differ between tasks requiring different muscle activation patterns, which may help to facilitate the coactivation of cortical representations of muscles involved in the task. For example, reductions in the magnitude of SICI have been observed in control of a target muscle when a synergistic muscle is concurrently activated (Devanne et al. 2002; Kouchtir-Devanne et al. 2012). In support of this, we observed a progressively greater reduction in SICI from rest to isolated index finger abduction to synergistic precision grip. However, the extent of disinhibition in an active muscle observed by us was greater than reported previously (Kouchtir-Devanne et al. 2012), with SICI almost completely absent during index finger abduction and with facilitation of the test MEP during precision grip. Contraction intensities and TMS characteristics were similar between studies, so it is unlikely that they would have contributed to these differences. One possible explanation for these variations between studies could relate to differences in task performance, with the current study using a constant contraction force between tasks (i.e., 5% MVC) and the previous study using constant EMG (Kouchtir-Devanne et al. 2012). As a result, normalized prestimulus EMG was significantly greater (~6%) during precision grip than during index finger abduction in the present study. However, subsequent analysis of these data in a subgroup of subjects with similar EMG between tasks showed similar SICI modulation compared with the original subject cohort, suggesting variations in muscle activation do not confound our findings. Nonetheless, our findings support previous studies suggesting that a progressively greater reduction in SICI occurs in tasks requiring the fine coordination of multiple task-related muscles.

In addition to SICI, Kouchtir-Devanne et al. (2012) also found that LICI was modulated by the task performed, with paired-pulse TMS measurements during precision grip showing a facilitation of the test MEP (Kouchtir-Devanne et al. 2012). Although we found that LICI was altered by muscle activation, this was not different between index finger abduction and precision grip, demonstrating a lack of task specificity. These findings suggest that LICI is insensitive to the demands of the task under the conditions of the present study. Given that the experimental conditions (contraction and TMS intensities) were similar between this and the previous study by Kouchtir-Devanne et al. (2012), we can only speculate as to why the two studies have produced divergent findings. One possible reason is related to differences in the requirements of the precision grip task. For example, Kouchtir-Devanne et al. (2012) performed a precision grip using an unsupported cylinder held vertically between the thumb and index finger, and it is possible that this task required a higher level of functional coupling between the two digits compared with the fixed manipulandum used in the present study.

Task-Related Variations in Presynaptic Motor Cortex Inhibition (LICI-SICI Interactions)

All previous investigations have assessed task-related changes in postsynaptic SICI and LICI, whereas the current study examined the presynaptic interaction between SICI and LICI during different tasks. This interaction is seen as a reduction in the magnitude of SICI when assessed in the presence of LICI (Sanger et al. 2001) and is thought to represent activation of presynaptic GABA subtypes-receptors on the terminal of SICI neurons by LICI collaterals (McDonnell et al. 2006; Muller-Dahlhaus et al. 2008; Sanger et al. 2001; Werhahn et al. 1999). Although the functional relevance of this presynaptic inhibition is unclear, deficits have been observed in subjects with Parkinson’s disease (Chu et al. 2009), and a role in sensorimotor organization has been suggested (Rosenkranz et al. 2008, 2009; Rosenkranz and Rothwell 2003, 2004). In resting muscle, we observed the expected reduction in SICI in the presence of LICI at ISIs of 100 (LICI100SICI) and 150 ms (LICI150SICI) compared with SICI in isolation (baseline SICI and SICIadj100/SICIadj150; Fig. 4), although the effect was more pronounced at 100 ms. Two previous assessments of ISI-dependent changes in the LICI-SICI interaction in resting muscle have reported reduced SICI only at 100 ms (Chu et al. 2008) and at both 100 and 150 ms (Cash et al. 2010). These conflicting findings introduced uncertainty as to the duration of presynaptic motor cortex inhibition in humans. In support of Cash et al. (2010), our observed disinhibition of SICI by LICI at both intervals suggests that presynaptic inhibition is in effect for at least 150 ms after the activation of LICI circuitry in humans.

In active muscle, the interpretation of the response to triple-pulse TMS is complicated by measurements of baseline SICI being markedly disinhibited, making further reductions in SICI difficult to observe. Nonetheless, during index finger abduction, SICI was significantly reduced (relative to baseline SICI and SICIadj150) when preceded by LICI at an ISI of 150 ms. In contrast, SICI was not influenced (relative to baseline SICI and SICIadj100/SICIadj150) by LICI during both tasks at the 100-ms ISI or during the precision grip task at the 150-ms ISI. These findings suggest that for measurements assessed at 100 ms or during precision grip at 150 ms, presynaptic mechanisms are unlikely to contribute to task-dependent changes in postsynaptic motor cortex inhibition observed during baseline SICI measurements (Ni et al. 2011b; Sanger et al. 2001). However, our findings also suggest that the disinhibition of baseline SICI observed during index finger abduction is associated with an increase in the activity of GABA- mediated presynaptic motor.
Timing-Dependent Variations in Intracortical Inhibition

Within the current study, one of the most notable findings was that task-dependent changes in LICI differed between ISIs. In these data, the transition from resting to active muscle produced an increase in inhibition assessed using the 100-ms ISI but a decrease in inhibition assessed using the 150-ms ISI. These findings are inconsistent with previous work for the 100-ms ISI (Hammond and Vallence 2007; McNeil et al. 2011) but are novel observations for the 150-ms ISI. In addition to these timing-dependent effects on LICI, effects of task on LICI-SICI interactions also varied between ISIs (during index finger abduction, inhibition was significantly reduced during LICI-SICI150 but not LICI-SICI100), and Stim100 was significantly greater than Stim150. Because the conditioning TMS stimuli (100–105% RMT) are used, whereas LICI at 150 ms is not (Vallence et al. 2014); and LICI at 100 ms is increased by continuous theta burst stimulation applied to the cerebellum, whereas LICI at 150 ms is unaffected (Koch et al. 2008). If measurements at different ISIs do represent activation of different cortical circuits, our findings could also reflect independent sensitivities of these circuits to voluntary contraction, possibly suggesting unique roles in motor control. This possibility remains to be explored.

In conclusion, our results demonstrate strong task-related variations in postsynaptic inhibition (SICI) but limited task-related variations in presynaptic inhibition (LICI-SICI interaction). Whereas SICI was progressively reduced from rest to index finger abduction to precision grip, LICI was only sensitive to muscle activation, and not the way in which the muscle was activated. Furthermore, task-related modulation in postsynaptic motor cortex inhibition was only observed during index finger abduction using a 150-ms ISI, suggesting a limited involvement of postsynaptic mechanisms in the task-dependent disinhibition of motor cortex. Finally, timing-dependent variations in the effect of muscle activation on LICI and LICI-SICI interactions may further support previous suggestions that nonidentical processes contribute to LICI at different ISIs. Because most previous studies have been performed in resting muscle, these findings provide new insight into the functional role of these inhibitory circuits, and how they interact, during the performance of different motor tasks.

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

AUTHOR CONTRIBUTIONS
G.M.O., M.C.R., and J.G.S. conception and design of research; G.M.O. performed experiments; G.M.O. and J.G.S. analyzed data; G.M.O., M.C.R., and J.G.S. interpreted results of experiments; G.M.O. prepared figures; G.M.O., M.C.R., and J.G.S. drafted manuscript; G.M.O., M.C.R., and J.G.S. edited and revised manuscript; G.M.O., M.C.R., and J.G.S. approved final version of manuscript.

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