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

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Opie GM, Ridding MC, Semmler JG. Task-related changes in intracortical inhibition assessed with paired- and triple-pulse transcranial magnetic stimulation. J Neurophysiol 113: 1470–1479, 2015. First published December 4, 2014; doi:10.1152/jn.00651.2014.—Recent research has demonstrated a task-related modulation of postsynaptic intracortical inhibition within primary motor cortex for tasks requiring isolated (abduction) or synergistic (precision grip) muscle activation. The current study sought to investigate task-related changes in pre- and postsynaptic intracortical inhibition in motor cortex. In 13 young adults (22.5 ± 3.5 yr), paired-pulse transcranial magnetic stimulation (TMS) was used to measure short (SICI)- and long-interval intracortical inhibition (LICI) (i.e., postsynaptic motor cortex inhibition) in first dorsal interosseous muscle, and triple-pulse TMS was used to investigate changes in SICI-LICI interactions (i.e., presynaptic motor cortex inhibition). These measurements were obtained at rest and during muscle activation involving isolated abduction of the index finger and during a precision grip using the index finger and thumb. SICI was reduced during abduction and precision grip compared with rest, with greater reductions during precision grip. The modulation of LICI during muscle activation depended on the interstimulus interval (ISI; 100 and 150 ms) but was not different between abduction and precision grip. For triple-pulse TMS, SICI was reduced in the presence of LICI at both ISIs in resting muscle (reflecting presynaptic motor cortex inhibition) but was only modulated at the 150-ms ISI during index finger abduction. Results suggest that synergistic contractions are accompanied by greater reductions in postsynaptic motor cortex inhibition than isolated contractions, but the contribution of presynaptic mechanisms to this disinhibition is limited. Furthermore, timing-dependent variations in LICI provide additional evidence that measurements using different ISIs may not represent activation of the same cortical process.

transcranial magnetic stimulation; paired-pulse TMS; triple-pulse TMS; task; γ-aminobutyric acid

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 GABAergic 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 GABAergic 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 GABAB 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 (Berdardelli 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 (Kouchtrir-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 (Kouchtrir-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 al. 2012).
2006; Muller-Dahlhaus et al. 2008; Ni et al. 2011a; Sanger et al. 2001; Werhahn et al. 1999). This presynaptic interaction between SICI and LICI is impaired in Parkinson’s disease patients, and this may contribute to their movement deficits (Chu et al. 2009). However, these previous studies have largely examined presynaptic motor cortex inhibition in resting muscles, and it is unknown whether presynaptic motor cortex inhibition is modulated during the performance of different tasks and whether this is related to task-dependent changes in postsynaptic intracortical inhibition.

The main aim of the current study was therefore to investigate task-related variations in pre- and postsynaptic GABA-mediated intracortical inhibition. This was accomplished by using paired- and triple-pulse TMS to examine SICI, LICI, and LICI-SICI interactions in first dorsal interosseous muscle (FDI) when it was resting or when it was active during isolated index finger abduction or precision grip (involving synergistic opposition of the index finger and thumb). Given that presynaptic motor cortex inhibition may be important for fine motor control (Chu et al. 2009), we would expect to see greater alterations in presynaptic and postsynaptic motor cortex inhibition during more demanding precision grip tasks. In addition, because the time course of presynaptic motor cortex inhibition in humans is not clear (Cash et al. 2010; Chu et al. 2008), a secondary aim was to compare any task-related changes in paired- and triple-pulse TMS measurements using two commonly used ISIs (100 and 150 ms).

METHODS

Thirteen young (22.3 ± 3.8 yr; mean ± SD) healthy subjects were recruited from the university and wider community to participate in the current study. Exclusion criteria included a history of neurological or psychiatric disease, or current use of psychoactive medication (sedatives, antipsychotics, antidepressants, etc.). Hand preference and laterality were assessed using the Edinburgh Handedness Inventory (Oldfield 1971). Each subject provided written, informed consent prior to participation. All experimentation was approved by the University of Adelaide Human Research Ethics Committee and conducted in accordance with the Declaration of Helsinki.

Experimental Arrangement

For the duration of the experiment, subjects were seated in a comfortable chair with their right arm abducted ∼45° at the shoulder. This allowed the forearm and hand to sit comfortably on an arm support placed next to them. Surface electromyography (EMG) was used to record responses from the FDI muscle of the right hand. Two Ag-AgCl electrodes (diameter 3.2 cm) were attached to the skin over the muscle in a belly-tendon montage, with a grounding strap around 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. 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 subject’s 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; Stim$_{1mV}$). 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; Stim$_{1mV}$). Representative data from a single subject for each of these experimental conditions in 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 Stim$_{150}$ and Stim$_{150}$ could account for changes in SICI observed during triple-pulse TMS. Therefore, additional measurements of SICI using Stim$_{100}$ (SICI$_{adj100}$) and Stim$_{150}$ (SICI$_{adj150}$) for the test stimulus were recorded as control states (conditions E and F, respectively). We refer to the test MEP generated during SICI$_{adj100}$ and SICI$_{adj150}$ as MEP$_{adj100}$ and MEP$_{adj150}$, 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 (SICI$_{adj100}$/adj150) and triple-pulse stimulation (LICI$_{adj}$SICI/LICI$_{adj150}$SICI), 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. Stim$_{1mV}$, Stim$_{100}$, and Stim$_{150}$ 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$_{rm}$), with factors of test stimulus condition (Stim$_{1mV}$, Stim$_{100}$, and Stim$_{150}$) 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$_{rm}$ and Fisher’s PLSD post hoc test.

**Mixed-model analysis** was used to investigate the effects of test MEP condition (MEP$_{1mV}$, MEP$_{adj100}$, MEP$_{adj150}$, MEP$_{100}$, and MEP$_{150}$) 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, SICI$_{adj}$, 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

**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 MEP$_{1mV}$</td>
<td></td>
<td></td>
<td></td>
<td>Stim$_{1mV}$</td>
</tr>
<tr>
<td>B SICI</td>
<td></td>
<td></td>
<td></td>
<td>Stim$_{1mV}$</td>
</tr>
<tr>
<td>C LICI$_{100}$</td>
<td>120% RMT</td>
<td></td>
<td></td>
<td>Stim$_{100}$</td>
</tr>
<tr>
<td>D LICI$_{150}$</td>
<td></td>
<td></td>
<td></td>
<td>Stim$_{150}$</td>
</tr>
<tr>
<td>E MEP$_{adj100}$</td>
<td>120% RMT</td>
<td></td>
<td></td>
<td>Stim$_{100}$</td>
</tr>
<tr>
<td>F MEP$_{adj150}$</td>
<td></td>
<td>80% AMT</td>
<td></td>
<td>Stim$_{150}$</td>
</tr>
<tr>
<td>G SICI$_{adj100}$</td>
<td></td>
<td>80% AMT</td>
<td></td>
<td>Stim$_{100}$</td>
</tr>
<tr>
<td>H SICI$_{adj150}$</td>
<td></td>
<td>80% AMT</td>
<td></td>
<td>Stim$_{150}$</td>
</tr>
<tr>
<td>I Test MEP$_{1mV}$</td>
<td>120% RMT</td>
<td></td>
<td></td>
<td>Stim$_{1mV}$</td>
</tr>
<tr>
<td>J Test MEP$_{100}$</td>
<td></td>
<td>80% AMT</td>
<td></td>
<td>Stim$_{100}$</td>
</tr>
<tr>
<td>K LICI$_{adj100}$/SICI</td>
<td>120% RMT</td>
<td></td>
<td></td>
<td>Stim$_{100}$</td>
</tr>
<tr>
<td>L LICI$_{adj150}$/SICI</td>
<td></td>
<td>80% AMT</td>
<td></td>
<td>Stim$_{150}$</td>
</tr>
</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 (Stim$_{1mV}$) or when preceded by either CS100 (Stim$_{100}$) or CS150 (Stim$_{150}$). 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.

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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-
100). As expected, these effects were driven by MEPadj100 and
stimulus conditions (MEP100, and MEP150) were found between stimulus conditions
or tasks (all P values $<0.05$), suggesting that these were well
between ISIs ($F_{2,49} = 96.7, P < 0.01$) 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
precision grip showed that LICI100 was not differentially af-
fected by the type of task performed ($P = 0.1$). In contrast, for

### Intracortical Inhibition

Representative data from a single subject in resting FDI are
subject demonstrated reduced SICI in the
subpopulation showed results similar to the those for the
original sample, with SICI of 98.4 [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 ($F_{1,249} = 90.7, P < 0.01$) 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 signif-
icantly 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 af-
affected by the type of task performed ($P = 0.1$). In contrast, for

### Table 2. Test MEP characteristics

<table>
<thead>
<tr>
<th>Condition</th>
<th>MEP1mV (CI)</th>
<th>MEPadj100 (CI)</th>
<th>MEPadj150 (CI)</th>
<th>MEP100 (CI)</th>
<th>MEP150 (CI)</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>65 [61, 69]</td>
<td>73 [68, 77]</td>
<td>73 [69, 78]</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>46 [41, 50]</td>
<td>64 [59, 70]</td>
<td>50 [43, 57]</td>
</tr>
</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. #P < 0.05 compared with Stim1mV, and Stim150.
Task-related changes in intracortical inhibition

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 LICI<sub>150</sub> in resting muscle during SICI<sub>adj100</sub> (i.e., when SICI was reassessed using the increased test TMS intensity required for production of reduced inhibition relative to both baseline (EMD: 28.9%, 95% CI [6.2, 19.5], P = 0.6), whereas triple-pulse TMS produced reduced inhibition relative to both baseline (EMD: 28.9%, 95% CI [6.2, 19.5], P = 0.6) and SICI<sub>adj150</sub> (EMD: 35.5%, 95% CI [7.7, 63.4], P < 0.01). However, during precision grip, the magnitude of inhibition did not vary between stimulation states. Task-related comparisons within each stimulation state showed that the magnitude of SICI<sub>adj150</sub> was progressively reduced from rest to index finger abduction (EMD: 25.7%, 95% CI [14.5, 36.9], P < 0.01) and precision grip (EMD: 27.1%, 95% CI [10.5, 43.8], P < 0.01). In contrast, during triple-pulse TMS, inhibition was significantly greater at rest compared with both abduction (EMD: 48.3%, 95% CI [21.0, 75.5], P < 0.01) and precision grip (EMD: 45.9%, 95% CI [24.3, 67.4], P < 0.01), but differences between abduction and precision grip were not significant. The absolute change in SICI, relative to baseline, was significant in resting muscle during SICI<sub>adj150</sub> (P < 0.004), but for both rest

### 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>ICI&lt;sub&gt;100&lt;/sub&gt;</td>
<td>9.4 [6.4,12.4]</td>
<td>16 [12.2,19.8]</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>SICI&lt;sub&gt;adj100&lt;/sub&gt;</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>
<tr>
<td>SICI&lt;sub&gt;adj150&lt;/sub&gt;</td>
<td>10.7 [7.8,13.7]</td>
<td>23 [12.7,33.2]</td>
<td>0.02</td>
</tr>
<tr>
<td>Test MEP</td>
<td>9.2 [6.2,12.3]</td>
<td>21.8 [12.8,30.8]</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>LICI&lt;sub&gt;150&lt;/sub&gt;</td>
<td>10.6 [7.6,13.7]</td>
<td>21.3 [15.0,27.7]</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Test MEP</td>
<td>9.4 [6.4,12.2]</td>
<td>21.1 [14.6,27.7]</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Values are means [95% CI lower limit, upper limit]. EMG, electromyography signal.

*Fig. 3. Task- and timing-dependent variations in the magnitude of LICI. Data show measurements of LICI using interstimulus intervals of 100 (solid bars) and 150 ms (open bars) during relaxation of the first dorsal interosseous (FDI) muscle, although no differences in this effect were found between all three task conditions during triple-pulse TMS. The absolute change in SICI, relative to baseline, was significant for all tasks during SICI<sub>adj150</sub> (all P values <0.004) but only in resting muscle during LICI<sub>100</sub>SICI (P < 0.004; Fig. 4B).

The effect of LICI on SICI at 150 ms is shown in Fig. 4C. Significant main effects of stimulation state (F<sub>2,286</sub> = 8.5, P < 0.01) and task (F<sub>2,339</sub> = 135.6, P < 0.01) were found, and there was a significant interaction (F<sub>4,277</sub> = 6.5, P < 0.01). In resting muscle, inhibition recorded during SICI<sub>adj150</sub> was significantly reduced compared with baseline (EMD: 19.5%, 95% CI [10.8, 28.3], P < 0.01), whereas inhibition recorded during triple-pulse TMS was reduced relative to both baseline (EMD: 32.5%, 95% CI [23.7, 41.3], P < 0.01) and SICI<sub>adj150</sub> (EMD: 13.0%, 95% CI [3.5, 22.4], P < 0.01). During index finger abduction, SICI<sub>adj150</sub> was not different from baseline (EMD: 6.7%, 95% CI [6.2, 19.5], P = 0.6), whereas triple-pulse TMS produced reduced inhibition relative to both baseline (EMD: 28.9%, 95% CI [6.2, 19.5], P = 0.6) and SICI<sub>adj150</sub> (EMD: 35.5%, 95% CI [7.7, 63.4], P < 0.01). However, during precision grip, the magnitude of inhibition did not vary between stimulation states. Task-related comparisons within each stimulation state showed that the magnitude of SICI<sub>adj150</sub> was progressively reduced from rest to index finger abduction (EMD: 25.7%, 95% CI [14.5, 36.9], P < 0.01) and precision grip (EMD: 27.1%, 95% CI [10.5, 43.8], P < 0.01). In contrast, during triple-pulse TMS, inhibition was significantly greater at rest compared with both abduction (EMD: 48.3%, 95% CI [21.0, 75.5], P < 0.01) and precision grip (EMD: 45.9%, 95% CI [24.3, 67.4], P < 0.01), but differences between abduction and precision grip were not significant. The absolute change in SICI, relative to baseline, was significant in resting muscle during SICI<sub>adj150</sub> (P < 0.004), but for both rest
and index finger abduction during LICI_{150}SICI (P < 0.004; Fig. 4D). When triple-pulse TMS was applied using the 100-ms ISI, normalized prestimulus rmsEMG amplitude was ~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 pre-
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 at the presence of LICI (Sanger et al. 2001) and is thought to represent activation of presynaptic GABAB 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 (LICI100\textsubscript{SICI}) and 150 ms (LICI\textsubscript{150}\textsubscript{SICI}) compared with SICI in isolation (baseline SICI and SICIadj\textsubscript{100}/SICIadj\textsubscript{150}; 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 SICIadj\textsubscript{150}) when preceded by LICI at an ISI of 150 ms. In contrast, SICI was not influenced (relative to baseline SICI and SICIadj\textsubscript{100}/SICIadj\textsubscript{150}) 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\textsubscript{A}-mediated presynaptic motor
cortex inhibition at a latency of 150 ms (Chin et al. 2012; Muller-Dahlhaus et al. 2008; Ni et al. 2011b; Sanger et al. 2001).

As mentioned above, no study has specifically assessed the effect of muscle activation on presynaptic motor cortex inhibition. However, one study has investigated changes in SICI during the CSP. Using an index finger abduction task at 20% MVC, Ni et al. (2007) measured SICI at three time points within the CSP, two of which (110 and 140 ms) were comparable to the intervals investigated by the current study. Relative to measurements in resting muscle, this previous study found significant reductions in SICI at both intervals (Ni et al. 2007). The timing-dependent nature of our effects of muscle activation on LICI-SICI interactions therefore only partially supports these findings. Despite this, comparisons between the two studies are limited due to methodological differences, including differences in contraction intensity (5% MVC by us, 20% MVC by Ni et al.), variations in the intensity of the conditioning stimulus (to activate SICI circuitry; 80% AMT by us, 95% AMT by Ni et al.), and the use of a different ISI to assess SICI (2 ms by us, 2.5 ms by Ni et al.).

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 used to activate LICI circuitry within the current study (i.e., 120% RMT) could be expected to elicit a CSP of ~150 ms (Chin et al. 2012), resolution of the CSP and the onset of post-CSP disinhibitory events (Chin et al. 2012) could be suggested to explain these timing-dependent effects. However, we found no evidence of EMG activity prior to the test stimulus for LICI150, so it is reasonable to suggest that the test stimulus for both LICI and LICI-SICI measurements was applied during the CSP, suggesting this mechanism is unlikely to explain our findings.

Alternatively, our timing-dependent effects of task on LICI and LICI-SICI interactions may provide further evidence for suggestions that LICI at different ISIs may have contributions from nonidentical cortical circuits. Although the ISIs that contribute to LICI (i.e., >50 ms; Brasil-Neto et al. 1995; Inghilleri et al. 1993) are often assumed to represent activation of the same cortical processes, a growing body of evidence suggests that this may not be an appropriate assumption. For example, LICI inhibits SICI at 100 ms but not 150 ms in resting muscle (Chu et al. 2008; but see Cash et al. 2010 and the current study for opposing findings); ischemic nerve block increases LICI at 150 ms but not 80 ms (Vallence et al. 2012); LICI at 100 ms is apparent when low-intensity conditioning 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, a task-related modulation in presynaptic motor cortex inhibition was only observed during index finger abduction using a 150-ms ISI, suggesting a limited involvement of presynaptic 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 many 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.