Clinical Neurophysiology 118 (2007) 1044–1052

www.elsevier.com/locate/clinph

Cortical control of muscle relaxation: A lateralized readiness potential (LRP) investigation

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Accepted 7 February 2007

Abstract

Objective: We used the lateralized readiness potential (LRP) to investigate cortical mechanisms underlying the termination of muscle contraction. Active suppression and withdrawal of activation have been proposed as underlying mechanisms in isotonic and isometric relaxation.
Methods: Experiment 1 investigated isotonic wrist extension/release from extension. Experiment 2 investigated isometric activation/relaxation of a pinch grip. Tasks were performed with left and right hands and cued auditorily at variable intervals. EEG was recorded from 128 electrodes and processed to derive the LRP timelocked to the onset and offset of muscle contraction.
Results: LRPs for isotonic activation and relaxation were of identical amplitude at electrodes overlying the motor cortex, but differed at frontal locations due to higher amplitude re-afferent activity during activation. The isometric LRP was significantly smaller during relaxation than during activation, without differences in scalp distribution.
Conclusion: The LRP findings confirm differences between isotonic and isometric relaxation, which may be partly explained by the need to suppress a stretch reflex in the former condition. The presence of an LRP associated with isometric relaxation reveals active preparation in the motor cortex, indicating that muscle relaxation in the isometric task cannot be explained solely by withdrawal of activation.
Significance: High-density LRP recordings isolate different cortical mechanisms underlying the termination of muscle contraction.

Keywords: EEG; Lateralized readiness potential; Movement-related potentials; Muscle relaxation; Inhibition

1. Introduction

Normal movement requires coordinated activation and relaxation of muscles. In a variety of neurological movement disorders, inadequate relaxation of muscle contributes to the impairment of voluntary movement. In particular, this is the case in dystonia, but impaired relaxation is also thought to be relevant to the parkinsonian movement disorder. As observed by Wing (1988) and by Kunesch et al. (1995), there is not only a slow build-up of force in Parkinson's disease, but an even slower release of force. Corcos et al. (1996) have shown that dopaminergic therapy gives greater improvement of the rate of muscle relaxation than of the rate of active muscle contraction. Information concerning muscle relaxation and the control of force release has been gained from measurements following a phasic voluntary muscle contraction such as a brief squeeze (Wing, 1988; Kunesch et al., 1995). Increasingly, studies have investigated the voluntary termination of a sustained contraction. Complementary measurements of movement-related EEG potentials during the voluntary

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1388-2457/$32.00
doi:10.1016/j.clinph.2007.02.002

act of muscle relaxation have enabled a comparison between cortical mechanisms of muscle activation and relaxation (Terada et al., 1995; Rothwell et al., 1998; Yazawa et al., 1999).

To date, investigations of muscle activation and relaxation using movement-related EEG potentials have been limited to recordings of the readiness potential in self-paced tasks. For movements involving isotonic muscle contraction, the readiness potentials associated with wrist extension (muscle activation) and passive wrist flexion (muscle relaxation) have been shown to be remarkably similar (Terada et al., 1995; Yazawa et al., 1999). This result can be explained by the existence of corticomotor neurons projecting onto spinal inhibitory interneurons (Cheney and Fetz, 1985; Lemon et al., 1987; Schmidt and McIntosh, 1990). However, Rothwell et al. (1998) used a task with isometric pinch grip activation and relaxation. In this task, the terminal segment of the readiness potential, measured at lateral electrode sites and presumed to be generated by the primary motor cortex, was reduced in amplitude for muscle relaxations. Based on these different findings between tasks with isometric and isotonic contractions, the authors proposed another mechanism for force release involving the withdrawal of excitatory input to the motor cortex.

Rothwell et al. (1998) did not make strong claims as to how well isotonic and isometric tasks dissociate the two mechanisms of active inhibition and withdrawal of facilitation. One reason for caution was the recognition that with both muscle activation and relaxation, there was activity arising from frontal midline structures such as the supplementary motor area. This activity overlapped with the motor cortex activity that was of primary interest and hindered the quantification of that activity. Moreover, it was difficult to know how the strength of the midline activity might be affected by differences in task difficulty between the activation and termination of an isotonic and an isometric contraction.

Against this background, we re-addressed the mechanisms underlying voluntary muscle relaxation in two experiments, one involving wrist extension/flexion (like Terada et al., 1995) and the other involving pinch activation/relaxation (like Rothwell et al., 1998). These experiments differed from previous approaches in the following respects. First, instead of self-paced muscle activation and relaxation, we examined these acts under externally (auditorily) cued conditions. Under such conditions, the midline activation associated with self-determined timing of the movement is much reduced (Deiber et al., 1991). Second, we had subjects perform the two tasks with the left and right hand separately to enable derivation of the lateralized readiness potential (LRP). The LRP captures lateralized movement-related activity arising from the frontal convexity by means of a subtraction between homologous electrodes contralateral and ipsilateral to the side of movement (Eimer and Coles, 2003). Combining such subtractions from left and right hand movement conditions removes residual stimulus-related activity associated with the signal that instructed subjects to activate or relax. Finally, EEG was recorded with high spatial resolution, which allowed us to better evaluate whether the activity associated with muscle relaxation has the same spatial distribution as the activity associated with muscle activation.

2. Methods

Two experiments were conducted with EEG recordings during muscle activation and muscle relaxation tasks. In Experiment 1, muscle activation and relaxation were performed in an isotonic manner with wrist extension movements and subsequent release from extension. In Experiment 2, muscle activation and relaxation were performed in an isometric manner with pinch hold and release. In both experiments, surface electromyography (EMG) established muscle relaxation. The timing of activation and relaxation was derived from an accelerometer signal in Experiment 1, and from a load cell force signal in Experiment 2.

2.1. Participants

In Experiment 1, there were eight participants (seven male). Age 24–45 years. Seven participants were right-handed. In Experiment 2, there were nine male participants, aged 21–37 years, with eight of them right-handed. Two persons participated in both experiments. All participants gave informed consent after an explanation of the study. The investigations were approved by the department's Ethics Committee.

2.2. Procedures

In Experiment 1 (isotonic contractions), activation required subjects to extend the wrist briskly on hearing a high-pitched tone. In this position, the hand was held against gravity in the horizontal plane (Fig. 1). Subsequent relaxation was signalled by a low-pitched tone that instructed subjects to let the hand drop suddenly without contraction of wrist flexors. High- and low-pitched tones

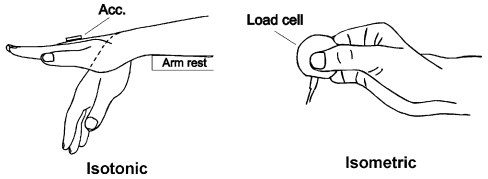

Fig. 1. In the isotonic task (left figure), the subject's hand was held extended in the horizontal plane and then released to a position with wrist flexion. In the corresponding activation condition, the hand was briskly extended to a horizontal position. An accelerometer (Acc.) attached to the dorsal surface of the hand was used to detect movement onsets. In the isometric task (right figure), the subject held a load cell between the thumb and index finger. The load cell was squeezed in the activation condition and released in the relaxation condition.

(1400 and 1000 Hz, respectively) were presented at a comfortable hearing level through a loudspeaker positioned 50 cm behind the subject. The interval between tones varied randomly between 2000 and 3500 ms. One experimental block consisted of 60 wrist extensions with the same number of passive flexions. Subjects performed three blocks with the right hand and three blocks with the left hand, yielding 180 trials for each hand. Left and right hand blocks were alternated and the order was balanced across subjects.

In Experiment 2 (isometric contractions), activation required subjects to squeeze a force transducer briskly between the thumb and index finger (Fig. 1) on hearing a high-pitched tone (1200 Hz). Pressure was maintained until a low-pitched tone (1000 Hz) cued the subject to release the squeeze (relaxation). Similar to Experiment 1, tones were separated by intervals that varied randomly between 2000 and 3500 ms. A single block consisted of 60 activations and the same number of relaxations. Subjects performed five blocks with the left and five with the right hand, yielding 300 trials for each hand. Left and right hand blocks were alternated and the order was balanced across subjects.

In both experiments, approximately 10 min of practice preceded data collection, during which subjects rehearsed activation and relaxation with instantaneous visual feedback of EMG activity on a computer monitor. In Experiment 2, the target grip force level required low to moderate force (15–25% of maximum grip force) and was indicated on the monitor concurrent with the EMG feedback. The computer monitor showing EMG and force or accelerometer signals was switched off during the experiment.

2.3. Data acquisition and processing

The electroencephalogram (EEG) was recorded continuously with Ag/AgCl electrodes from 126 scalp electrodes relative to an off-line averaged mastoids reference. Scalp electrodes were placed according to the 10-5 electrode system (Oostenveld and Praamstra, 2001), using a carefully positioned nylon cap. EEG signals were amplified with a bandpass of DC-128 Hz (DC-256 Hz Experiment 2) using a BioSemi Active-Two amplifier, and sampled at 512 Hz (Experiment 1) or 1024 Hz (Experiment 2). Surface electromyographic (EMG) activity was recorded using four pairs of Ag/AgCl electrodes. In Experiment 1, EMG was recorded from left and right forearm extensor (m. extensor carpi radialis) and flexor muscles (m. flexor carpi ulnaris). In Experiment 2, EMG was recorded from the thenar (m. abductor pollicis brevis) and the first dorsal interosseous muscle of each hand. EMG was recorded and stored together with the EEG. In Experiment 1, an accelerometer (Entran Sensors & Electronics, Fairfield, USA) attached to the dorsal surface of the hand detected movement onset. In Experiment 2, the output from a load cell (Novatech Measurements Ltd, Hastings, UK) signalled pinch force. This information was also sampled and stored with the EEG.

The continuous EEG recordings were segmented off-line into 1500 ms epochs (750 ms before and after onset of activation or relaxation). Individual epochs containing artefacts were rejected before averaging. These included eye blinks and trials in which antagonist contraction was evident during relaxation at the time of movement onset. Response-locked LRPs were calculated separately for activation and relaxation, whereby the activity at electrode sites ipsilateral to the responding hand was subtracted from the activity at contralateral electrode sites, yielding difference waveforms for left and right hand responses. These waveforms were averaged across response sides to obtain the LRP. To justify the use of the LRP, checks were implemented to ensure that left and right hemisphere contributions to the LRP were comparable (Oostenveld et al., 2003). The left and right motor cortex contributions were measured at electrodes C3 and C4 in data obtained through subtraction of left and right hand response conditions and were found to be of the same size in both experiments.

2.4. Data analysis

The strength of lateralized movement-related activity in activation and relaxation was quantified in terms of the amplitude of the LRP at peak latency, measured at the electrode site where it reached the highest amplitude. The amplitude was measured as the mean value of the signal in a time window of 10 ms around the peak latency. The baseline was defined as the mean amplitude between 400 and 200 ms before movement onset. Differences in amplitude of the LRP between activation and relaxation conditions were analysed with one-way ANOVAs for isotonic and isometric tasks separately. Differences in peak latency of the LRP relative to movement onset were analysed in the same way.

An additional analysis of variance assessed differences in the distribution of the LRP between activation and relaxation conditions. This analysis used amplitude values measured in the same time window of 10 ms as the above analysis on the LRP peak amplitude. These values were measured in a region of interest defined over the sensorimotor cortex, covered by a rectangular grid of $5 \times 7 = 35$ electrode locations. For locations in the grid not corresponding with actual electrodes, values were interpolated from the four nearest neighbouring electrodes (see Fig. 2). To eliminate confounds due to differences in amplitude of the LRP between activation and relaxation conditions (McCarthy and Wood, 1985), data were normalized using a vector scaling approach (Urbach and Kutas, 2002). Grid axes (medial–lateral and anterior–posterior) were treated as independent factors (designated ML and AP, respectively), while the Direction of movement (activation versus relaxation) was the repeated measure. To control for effects of non-sphericity in within-subject tests, degrees of freedom for F tests were corrected using the Greenhouse–Geisser correction.

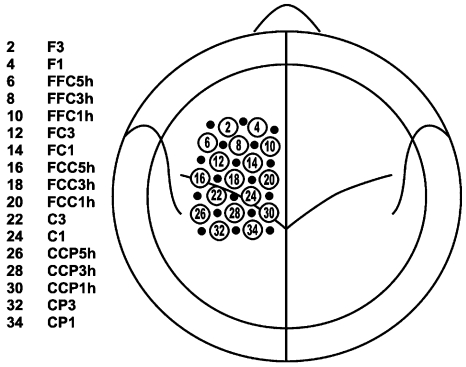

Fig. 2. Top view of a schematic head showing the location of electrodes used in the topographical analysis. Interpolated electrode positions are shown in black. Electrode labels according to the 10-5 system and corresponding numbers in the grid are listed on the left.

To support the interpretation of LRP distributions, we performed a dipole source analysis on the grand average LRP across tasks and activation/relaxation conditions. The grand average was created following a realignment of the four different datasets at the LRP peak latency (set to 0), measured at the electrode site where it reached highest amplitude. The main goal of dipole source analysis was to illustrate that the LRP can be decomposed in two main components that capture the same activity as found in dipole source analysis of the readiness potential. Recognition of their distinct scalp topographies facilitates the interpretation of the differences in scalp distribution between conditions. Dipole source analysis was not used for quantitative analyses, since simple reaction tasks produce much smaller LRP amplitudes than choice response tasks (cf. Praamstra and Seiss, 2005), prohibiting source analysis at the single subject level.

The computation of LRP scalp topographies and dipole source analysis were performed in Brain Electrical Source Analysis (BESA; MEGIS software, Gräfelfing, Germany). Dipole source analyses used the standard four-shell ellipsoidal head model implemented in BESA, with default conductivities. Since the LRP is a difference signal between left and right sensorimotor cortex, dipole source analysis required that the LRP was represented with opposite polarity over left and right hemisphere, as described in Praamstra et al. (1996). This enables modelling of the LRP with anti-symmetric sources in left and right hemisphere. Although this procedure yields bilateral sources (of identical strength), the LRP is commonly discussed as if generated in the hemisphere contralateral to movement. This is not strictly true since the LRP derivation is blind to the individual contributions from each hemisphere.

3. Results

3.1. EMG activity

Brisk wrist extension was associated with a phasic burst of activation of the m. extensor carpi radialis, followed by an activation plateau during the maintenance of the hand in the neutral position (see Fig. 3). The brief low amplitude activity in the recording over the wrist flexor (m. flexor carpi ulnaris) is likely due to volume conduction. More important, the wrist flexor muscle was silent during relaxation (see Fig. 3), since trials in which flexor activity was detected were excluded (20%; mean 35 ± 39).

During isometric pinch grip, there was simultaneous activation of the m. abductor pollicis brevis and the first dorsal interosseous muscle, which terminated together at the onset of relaxation. In this task, 6% of trials (mean 18 ± 40) were excluded due to an aberrant pattern of muscle relaxation. Muscle relaxation proceeded slower than muscle activation under both isotonic and isometric conditions, as can be observed in the EMG traces of Fig. 3 and in the accelerometer and force traces.

3.2. LRP peak amplitude and latency

Both activation and relaxation were accompanied by an LRP (Fig. 3). For isotonic movements, the maximum amplitude of the LRP was at CCP3h/4h electrode sites, immediately posterior to C3/C4. For isometric activation and relaxation the maximum LRP amplitude was at C3/C4 electrode sites. Measures of mean amplitude at peak latency and the peak latency for activation and relaxation waveforms are presented in Table 1. For isotonic movements, it is clear from Fig. 3 and Table 1 that the size of the LRP during relaxation is equal to that during activation ($F(1,7) < 1$). These results contrast with those for isometric contractions, in which the amplitude of the LRP for relaxation (-1.2 μV) was significantly smaller than that for activation (-1.9 μV) ($F(1,8) = 7.94$, $P < 0.05$).

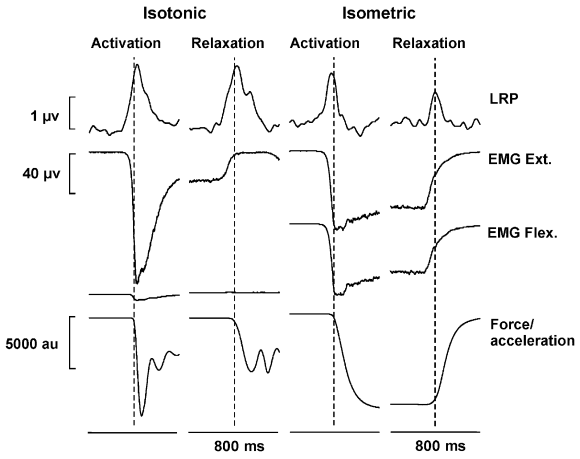

Fig. 3. The top row shows grand average LRP waveforms at CCP3h/CCP4h and C3/C4 electrode sites for the isotonic (left) and isometric (right) tasks, respectively. The middle two rows show EMG traces associated with activation and relaxation in isotonic extension/flexion (flexor carpi ulnaris and extensor carpi radialis) and in isometric pinch/release (abductor pollicis brevis and first dorsal interosseus). The bottom row shows movement onset/offset profiles for isometric and isotonic conditions, as obtained from accelerometer and load cell (au = arbitrary unit).

Table 1
Peak latency (ms) and amplitude (μV) of the LRP

	Isotonic task		Isometric task	
	Latency	Amplitude	Latency	Amplitude
Activation	24.7 ± 15.4	−2.4 ± 0.7	−19.4 ± 23.0	−1.9 ± 0.8
Relaxation	23.0 ± 27.2	−2.4 ± 0.9	10.6 ± 24.8	−1.2 ± 0.6

As to LRP peak latencies, there was no significant difference between activation (25 ms) and relaxation (23 ms) conditions ($F(1,7) < 1$) in the isotonic task. By contrast, the peak latency occurred earlier in activation (−19 ms) than in relaxation (11 ms) in the isometric task ($F(1,8) = 12.61$, $P < 0.01$). Taken together, the amplitude modulation of the LRP in the isometric task, without a similar modulation in the isotonic task, suggests the operation of different mechanisms for the termination of muscle activity.

3.3. LRP scalp distribution

Prior to quantitative analyses of the LRP scalp distribution between tasks and activation/relaxation conditions, the scalp distributions were inspected. The scalp distributions are represented in Fig. 4 aligned to their peak latency set at 0 ms. At peak latency the LRP shows, for each task and condition, a similar monopolar scalp distribution over the central scalp region. This distribution evolves to a dipolar field distribution with a gradient across the central sulcus, or somewhat more posterior (isotonic task), at latencies between 60 and 70 ms. Dipole source analysis on all the data pooled together is illustrated in Fig. 5, to show how the scalp distributions may be generated. The monopolar field distribution over the central scalp region is explained by a radial dipole suggesting a source in the crown of the precentral gyrus. The dipolar field across the central sulcus is explained by a tangential dipole. The depicted dipoles were localized in an initial analysis step with one regional source in each hemisphere, fitted in a time window from −50 to 100 ms. This step was followed by separate optimization of the orientation of the radial dipole pair and the tangential dipole pair. The resulting model had a goodness of fit >95% at the peak latencies of both its constituent components. Applied to the grand average datasets of the isotonic and isometric tasks, separately for activation and relaxation conditions, the fit was always >75%.

The analysis of the LRP scalp distribution was performed on amplitudes in a time window of 10 ms around the peak latency, measured at the electrode with the highest LRP amplitude, i.e., CCP3h/4h (isotonic task) and C3/C4 (isometric task). Within the 5 × 7 grid of electrodes covering the sensorimotor cortex scalp area, the LRP for isotonic movements displayed a relatively focal maximum at CCP3h/4h. As a result, there were significant amplitude gradients along the anterior–posterior (AP) axis ($F(1.50, 10.52) = 36.13$, $P < 0.001$) and the medial–lateral (ML)

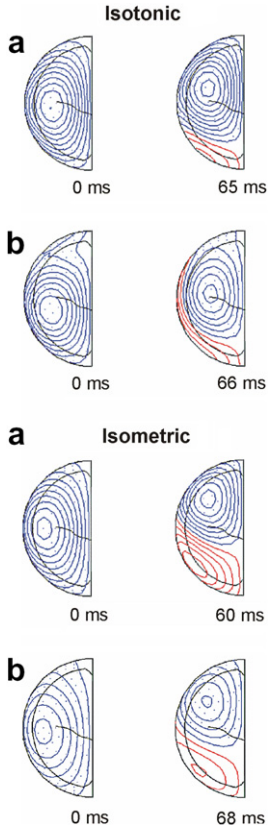

Fig. 4. Scalp distributions of the LRP in both tasks, for activation (a) and relaxation (b) conditions. The distributions are plotted at peak latency, set at 0 ms, showing a monopolar field distribution, and at the latency where re-afferent activity was best defined, characterized by a dipolar field distribution. Spacing of contour lines 0.20 μV.

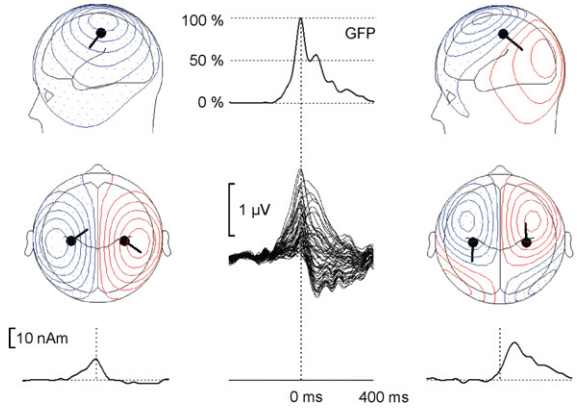

Fig. 5. Dipole source analysis of the LRP, using a bilateral-inverted projection of the LRP onto left and right sides of the head. The response-locked LRPs are represented in a butterfly plot and a global field power (GFP) plot (middle panel). The two dipoles in each hemisphere were optimized to explain movement-related activity (left panel), and movement-evoked or re-afferent activity (right panel). The time course of activation of each source is represented in the source waveforms displayed underneath the isopotential maps. The source of the movement-related activity peaks at 0 ms. The re-afferent source waveform peaks at ~70 ms. Spacing of contour lines 0.25 μV.

axis, ($F(2.10, 14.68) = 20.50$, $P < 0.001$), as well an interaction of AP and ML axes ($F(3.63, 25.42) = 7.61$, $P < 0.001$). A difference in scalp distribution between activation and relaxation conditions would manifest as an interaction of Direction with AP and/or ML axes. Such an interaction was found for Direction by AP axis ($F(2.80, 19.56) = 3.90$, $P < 0.05$). It was explained by a higher LRP amplitude for the activation than for the relaxation condition at electrodes anterior to CCP3h/4h, at which electrode they were identical.

The difference in distribution between activation and relaxation LRPs is illustrated in Fig. 6a, with scalp topographies of their subtraction and with waveforms at selected electrode sites. The figure shows the scalp topography of the subtraction at the peak latency of the LRP (0 ms). At this latency, the scalp topography is characterized by a dipolar field distribution across the central sulcus. As will be further addressed in the Discussion, the scalp distribution of the subtraction suggests that the difference between activation and relaxation conditions is explained by a difference in re-afferent feedback.

Similar analyses were performed for the task with isometric activation and relaxation. As in the isotonic task, there was a significant amplitude modulation along the anterior–posterior axis ($F(1.84, 14.68) = 16.70$, $P < 0.001$) and along the medial–lateral axis ($F(1.20, 9.62) = 21.09$, $P < 0.001$), with an expected interaction of AP and ML axes ($F(3.56, 28.50) = 2.91$, $P < 0.05$). However, in contrast to the isotonic task, there was no difference in distribution of the LRP between activation and relaxation conditions, since there was no significant interaction of the factor Direction with AP or ML axis. In accordance with the identical scalp distributions of activation and relaxation conditions at peak latency, their subtraction shows a monopolar maximum over the central scalp area at 0 ms (see Fig. 6b).

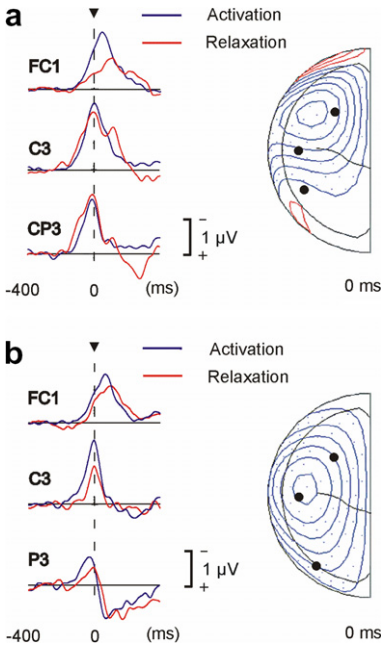

Fig. 6. Lateralized readiness potentials for activation and relaxation conditions in the isotonic task (a) and in the isometric task (b). The locations of the selected electrodes are indicated on the isopotential maps of the subtraction of activation and relaxation conditions. Isopotential maps are plotted at the peak latency of the LRP (0 ms). Spacing of contour lines 0.10 μV.

4. Discussion

Previous movement-related potential studies contrasting muscle activation and relaxation have used the readiness potential as an index of motor cortex activation (e.g., Terada et al., 1995; Rothwell et al., 1998; Yazawa et al., 1999). Since it is difficult to separate motor cortex and medial premotor cortex contributions to the readiness potential (Praamstra et al., 1996), these studies do not allow a sufficiently selective assessment of motor cortex activity during the termination of a muscle contraction. This problem is compounded by a difference in task difficulty between muscle activation and relaxation (Rothwell et al., 1998). Against this background, the present study used the lateralized readiness potential (LRP) to better isolate activity arising from the motor cortex and the convexity from activity in midline premotor structures. Another limitation of previous movement-related potential studies has been the virtually exclusive use of isotonic muscle activation and relaxation tasks. Only Rothwell et al. (1998) made recordings in an isometric task, yielding preliminary evidence from two participants that the readiness potential is of smaller amplitude during relaxation than during muscle activation. In the present study, therefore, muscle activation and relaxation were compared not only in an isotonic task, but also in an isometric task.

The results are in line with the earlier readiness potential findings of Rothwell et al. (1998) in finding clear differences between isotonic and isometric tasks. Since both studies used wrist movements for the isotonic task and a thumb–index finger pinch for the isometric task, one might consider that the differences are explained by the different effectors involved in the tasks. However, such an explanation is extremely implausible in view of the generally close similarity of movement-related EEG potentials elicited by different forearm movements and effectors.

The interpretation of differences in LRP scalp distribution between conditions was facilitated by the dipole source analysis of the LRP, but does not depend on it. The analysis separated two components. The first was explained by a radial dipole and peaked around the time of movement or force onset/offset. The second was explained by a tangential dipole with activity peaking ~70 ms later. Although these components are identified in lateralized potentials, they correspond well to sources identified in fMRI supported dipole source analysis of the readiness potential preceding self-paced movements (Toma et al., 2002) and in analyses of steady-state movement-related potentials (Gerloff et al., 1998). Supported by these analyses, the first com-

ponent is interpreted as premovement activity and activity associated with movement execution, the second as movement-evoked (re-afferent) activity. With respect to the concordance between dipole source analysis of lateralized potentials and the readiness potential, it should be kept in mind that the LRP represents differences in activity measured between left and right hemisphere. It does therefore not capture the bilateral contributions to premovement activity identified in analyses of the readiness potential (Toma et al., 2002; Cheyne et al., 2006).

The results of our study bear on the mechanisms that have been proposed to underlie muscle relaxation. Buccolieri et al. (2004) list three different possible mechanisms. The first involves the activation of cortico-motoneurons that project onto inhibitory spinal interneurons. The existence of this mechanism is well established by neurophysiological experiments in monkeys (Jankowska et al., 1976; Lemon et al., 1987). Some of the first movement-related potential studies of muscle relaxation (Terada et al., 1995; Yazawa et al., 1999) referred to this mechanism as the likely explanation for the largely similar readiness potentials for muscle activation and relaxation in an isotonic task. Our LRP results in the isotonic task strengthen this reasoning, given the identical LRPs during muscle activation and relaxation at electrode sites directly overlying the motor cortex. However, taking the LRP scalp distribution into account, there was a difference between activation and relaxation, probably due to stronger re-afferent proprioceptive activity for the activation condition. Proprioceptive cortical responses to passive movement have previously been shown to have the same dipolar field distribution across the central sulcus (Seiss et al., 2002). An explanation of the difference in scalp distribution in terms of a difference in proprioceptive feedback is consistent with the proposal that the descending corticospinal output in an isotonic relaxation task helps to suppress a stretch reflex in the wrist extensor muscles (Rothwell et al., 1998). As to the origin of re-afferent proprioception-related potentials there is evidence for the post-central sensory cortex (Mima et al., 1996; Hoshiyama et al., 1997; Oishi et al., 2004; Cheyne et al., 2006) as well as for a motor cortex contribution (Hoshiyama et al., 1997; Seiss et al., 2002; Cheyne et al., 2006). On the latter view, one would expect that the difference between activation and relaxation in our LRP results would be reflected in functional imaging findings of motor cortex activation in a similar task. In this respect, however, our results are not in accordance with Toma et al. (1999) who found primary motor cortex activity of the same strength for voluntary activation and relaxation performed in an isotonic manner, using fMRI.

The second mechanism postulated by Buccolieri et al. (2004) is the withdrawal of input from premotor areas to the primary motor cortex. Rothwell et al. (1998) had proposed this mechanism as one that operates specifically in an isometric task, and which would not involve preparation in the primary motor cortex, thus explaining the difference in size they found between readiness potentials for muscle activation and relaxation. Our results do not provide support for the operation of such a mechanism. In the isometric task, there was an identical distribution in activation and relaxation conditions, making it unlikely that the relative activation of pre- and primary-motor cortex was different between conditions. In the isotonic task, the difference between activation and relaxation was explained by activity with a dipolar field distribution, not likely originating from the premotor cortex.

The third mechanism indicated by Buccolieri et al. (2004) is an inhibition of motor cortical output mediated by inhibitory interneurons in the motor cortex. The operation of such a mechanism is supported by their own transcranial magnetic stimulation (TMS) experiments, testing short-latency intracortical inhibition (SICI) preceding muscle activation and relaxation. An increased SICI was found preceding the termination of a contraction, presumably contributing to the termination of corticospinal outflow. Although this mechanism reflects active preparation for the termination of a contraction within the motor cortex itself, it is not necessarily expressed in measurable EEG activity on the scalp (Toma et al., 1999). This is because the orientation of the inhibitory interneurons' dendrites would be more variable than the regular columnar orientation of pyramidal cells' dendritic trees, and form a closed field (Lorente de No, 1947; Lopes da Silva and van Rotterdam, 1993). It is nonetheless possible that the attenuated LRP during relaxation, in our isometric task, might reflect the operation of this third mechanism. In contrast to Buccolieri and co-workers, Begum et al. (2005) found a decreased SICI preceding relaxation of an isometric contraction and proposed that also in isometric tasks relaxation is achieved partly through excitation of cortico-motoneurons that project onto inhibitory spinal interneurons. Our LRP data in the isometric task are equally compatible with this view.

A fourth possible mechanism involved in the termination of muscle activity is suggested by the clinical phenomenon of negative myoclonus (Shahani and Young, 1976), caused by an interruption of tonic muscle activity. Intraoperative cortical stimulation studies have identified "negative motor areas", whose stimulation produces negative motor responses. Such areas have been identified both on the medial surface (Lüders et al., 1987; Lim et al., 1994) and the lateral surface of the frontal lobe (Kunieda et al., 2004; Rubboli et al., 2006). The investigation by Kunieda and co-workers recorded movement-related potentials from cortical sites adjacent to negative motor areas in the lateral premotor cortex. In contrast to the classical readiness potential, these movement-related potentials had a surface positive polarity preceding active movements (Kunieda et al., 2004). It is not known whether the negative motor areas would be recruited to voluntarily terminate a muscle contraction, or whether they would generate negative or positive potential shifts. The activity in negative motor areas would probably be measurable with scalp-recorded EEG. The fact that we did not detect activity

associated with muscle relaxation localized to the lateral premotor cortex thus suggests that negative motor areas may not be relevant to voluntary muscle relaxation.

5. Conclusions

The results of this investigation support the proposal that the termination of muscle contraction relies on different mechanisms depending on whether the task involves isotonic or isometric muscle contraction (Rothwell et al., 1998). However, they do not support that only the isotonic task requires active preparation in the motor cortex, contrasting with a mechanism of withdrawal of ongoing input to the motor cortex in the isometric task (Rothwell et al., 1998). This is because in the latter task version, the LRP was reduced in amplitude preceding relaxation compared to activation, but by no means absent. The small LRP associated with isometric relaxation might either reflect a descending discharge to the spinal level or the activity of cortical inhibitory interneurons. The relevance of such inhibitory interneurons to isometric muscle relaxation has been established by TMS paired-pulse protocols testing intracortical inhibition preceding relaxation (Buccolieri et al., 2004). Although the visibility of this interneuronal activity to EEG is uncertain (Lorente de No, 1947; Toma et al., 1999), it cannot be ruled out as the possible substrate of the small LRP preceding isometric relaxation.

Our LRP findings have greater specificity than previous readiness potential studies in this area, because the LRP derivation isolates the activity over the lateral convexity from simultaneous non-lateralized activity in the midline. Importantly, the LRP comprises not only the motor cortex activation associated with the control of a descending discharge, but captures also the activity in response to re-afferent feedback. These components are distinguishable in the scalp topography and are localized to the sensorimotor cortex. The separation of these components is facilitated by high-density recordings and supported the interpretation of LRP differences between isotonic and isometric activation/relaxation in the present experiments. These advantages make high-density recordings of the LRP a useful tool in further investigations of muscle relaxation in neurological movement disorders.

Acknowledgement

This work was funded by the Medical Research Council.

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