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Contrasting Properties of Motor Output from the Supplementary Motor Area and Primary Motor Cortex in Rhesus Macaques

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The goal of this study was to assess the motor output capabilities of the forelimb representation of the supplementary motor area (SMA) in terms of the sign, latency and strength of effects on electromyographic (EMG) activity. Stimulus triggered averages of EMG activity from 24 muscles of the forelimb were computed in SMA during a reach-to-grasp task. Poststimulus facilitation (PStF) from SMA had two distinct peaks (15.2 and 55.2 ms) and one poststimulus suppression (PStS) peak (32.4 ms). The short onset latency PStF and PStS of SMA were 5.5 and 16.8 ms longer than those of the primary motor cortex (M1). The average magnitudes (peak increase or decrease above baseline) of the short and long latency PStF and PStS from SMA at 60 μA were 13.8, 11.3 and −11.9% respectively. In comparison, M1 PStF and PStS magnitudes at 15 μA were 50.2 and −23.8%. Extrapolating M1 PStF magnitude to 60 μA yields a mean effect that is nearly 15 times greater than the mean PStF from SMA. Moreover, unlike M1, the facilitation of distal muscles from SMA was not significantly greater than the facilitation of proximal muscles. We conclude that the output from SMA to motoneurons is markedly weaker compared with M1 raising doubts about the role of SMA corticospinal neurons in the direct control of muscle activity.

Keywords: EMG, motor cortex, monkey, SMA, stimulus-triggered averaging

Introduction

The supplementary motor area (SMA) is located on the mesial wall of the hemisphere and is one of several secondary motor areas located in the primate frontal lobe that sends projections to the spinal cord (Dum and Strick, 1991; He *et al.*, 1995). SMA's overall termination pattern in the cervical enlargement of the spinal cord qualitatively resembles that from the primary motor cortex (M1), suggesting the generation of motor output from SMA via direct pathways independent of M1 (Dum and Strick, 1996; Rouiller *et al.*, 1996). Both M1 and SMA have terminations in the ventral horn, where it has been shown that M1 neurons have powerful monosynaptic connections with motoneurons. Corticomotoneuronal synaptic connections provide a direct input to motoneurons, which is thought to be important for the generation of independent finger movements (Kuypers, 1981; Porter and Lemon, 1993). While the monosynaptic linkages from M1 to spinal motoneurons of the hand motor nuclei in primates are common and have been demonstrated in great detail, such a direct linkage from SMA has only recently been identified. Using intracellular recording from motoneurons in macaque monkeys, Maier *et al.* (2002) provided evidence that some SMA efferents make monosynaptic connections with motoneurons, although EPSPs (excitatory postsynaptic potentials) recorded from SMA stimulation were only half as common as those from M1 stimulation. This suggests that SMA can act independently of M1 to influence the excitability of motoneurons in the control of movement.

Functionally, a variety of single unit recordings and brain imaging studies have demonstrated not only coactivation of SMA with M1 during various types of movement tasks, but also some unique functional properties of SMA and M1 (for a review, see Cheney *et al.*, 2004). Despite the potential importance of SMA in the production of forelimb movement through its corticospinal projections, few functional output studies of SMA exist. The purpose of this study was to assess the motor output capabilities of SMA, relative to M1, in terms of the sign (excitatory or inhibitory), latency and strength of poststimulus effects on electromyographic (EMG) activity of 24 forelimb muscles, including shoulder, elbow, wrist, digit and intrinsic hand muscles.

Materials and Methods

Behavioral Task and Surgical Procedures

Data were collected from two male rhesus monkeys (*Macaca mulatta*, ~9 kg, 6 years of age) that were trained to perform a reach-to-grasp task as described previously (Belhaj-Saïf *et al.*, 1998; McKiernan *et al.*, 1998). On completion of training, each monkey was implanted over the forelimb area of SMA with a magnetic resonance imaging (MRI) compatible cortical chamber allowing the exploration of a 30 mm diameter area of the left hemisphere. The centers of the chambers were stereotaxically implanted at anterior 13.4 mm (monkey B) and at anterior 12.9 mm (monkey Y) with an angle of 15° to the midsagittal plane. Chamber implantation and electrode placements were guided by structural MRIs obtained from a 3 Tesla Siemens Allegra system. Images were obtained with the monkey's head mounted in an MRI compatible stereotaxic apparatus so the orientation and location of the penetrations could be precisely estimated (Fig. 1). The dura was opened during chamber implantation to confirm the location of the central sulcus. The location of the central sulcus also aided in matching the electrode penetrations to the MR images.

EMG activity was recorded from 24 muscles of the forelimb using a modular subcutaneous implant method in which a pair of multi-stranded stainless steel wires (Cooner Wire, Chatsworth, CA) was implanted in each muscle and the wires were led subcutaneously to connectors on the forearm. The monkeys wore jackets to protect the implants. These procedures are described in detail in a previous paper (Park *et al.*, 2000). EMGs were recorded from five shoulder muscles: pectoralis major (PEC), anterior deltoid (ADE), posterior deltoid (PDE), teres major (TMAJ) and latissimus dorsi (LAT); seven elbow muscles: biceps short head (BIS), biceps long head (BIL), brachialis (BRA), brachioradialis (BR), triceps long head (TLON), triceps lateral head (TLAT) and dorso-epitrochlearis (DE); five wrist muscles: extensor carpi radialis (ECR), extensor carpi ulnaris (ECU), flexor carpi radialis (FCR), flexor carpi ulnaris (FCU) and palmaris longus (PL); five digit muscles: extensor digitorum communis (EDC), extensor digitorum 2 and 3 (ED 2,3), extensor digitorum 4 and 5 (ED 4,5),

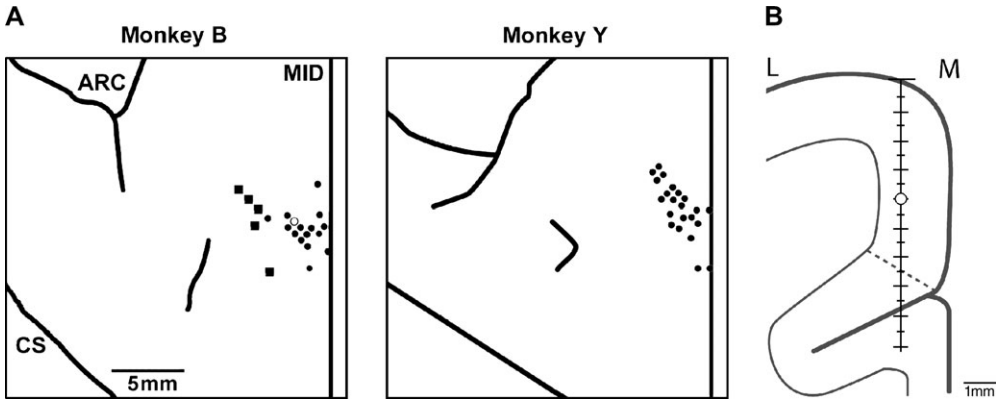

Figure 1. (*A*) Location of electrode tracks in the left hemisphere of the two monkeys from which SMA data was obtained. Tracks where StTA produced effects are marked by circles; the open circle in the surface map of monkey B and the tissue section drawing (*B*) indicates the site that produced the records shown in Figure 2. Tracks that produced no effects are indicated by filled squares. (*B*) Drawing of coronal section of the cortex based on reconstruction from MR images and electrophysiological data. The dotted line indicates the border between CMAd and SMA. Abbreviations: ARC, arcuate sulcus; CS, central sulcus: L, lateral; M, medial; MID, convexity of the cortex at the midline.

flexor digitorum superficialis (FDS) and flexor digitorum profundus (FDP); and two intrinsic hand muscles: abductor pollicis brevis (APB) and first dorsal interosseus (FDI). All surgeries were performed under deep general anesthesia and aseptic conditions. Postoperatively, monkeys were given an analgesic (Buprenorphine 0.5 mg/kg every 12 h for 3–4 days) and antibiotics (Penicillin G, Benzathaine/Procaine combination, 40 000 IU/kg every 3 days). All procedures were in accordance with the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) and the Guide for the Care and Use of Laboratory Animals, published by the US Department of Health and Human Services and the National Institutes of Health.

Data Recording

Electrode penetrations were made broadly throughout the extent of the forelimb representation of SMA in each animal (Luppino *et al.*, 1991; He *et al.*, 1995). The chamber coordinates of forelimb SMA were estimated from MRI scans. For cortical recording and stimulation, we used glass and mylar insulated platinum-iridium electrodes with typical impedances between 0.7–2 MΩ (Frederick Haer & Co., Bowdoinham, ME). The electrode was advanced with a manual hydraulic microdrive and stimulation was performed in all layers of the gray matter of SMA at 0.5 mm intervals, starting 0.5 mm below the first cortical electrical activity encountered. Sites below 6 mm were excluded of this analysis to avoid contamination from the dorsal cingulate motor area (CMAd) (Fig. 1). Cortical electrical activity and EMG activity were simultaneously monitored along with task related signals. Stimulus triggered averages (60 μA @ 7–15 Hz) of EMG activity were computed for 24 muscles of the forelimb from stimuli applied throughout all phases of the reach-to grasp task. The selection of 60 μA for SMA stimulation was based on an initial stimulus intensity study in which poststimulus effects at intensities from 15 to 60 μA were compared. Few effects were observed at 30 μA and below and effects remained largely weak at 40 μA. All StTAs were based on at least 2000 trigger events. Individual stimuli were symmetrical biphasic pulses (0.2 ms negative followed by 0.2 ms positive). EMGs were filtered from 30 Hz to 1 KHz, digitized at 4 kHz and full-wave rectified. Averages were compiled using an epoch of 60 ms length, extending from 20 ms before the trigger to 40 ms after the trigger. Epoch duration was lengthened to 120 ms (30 ms pre-trigger to 90 ms post-trigger) when it was observed that a second, long latency facilitation peak was often present. The 60 ms epoch was used for 19 electrodes tracks in monkey Y. The remaining tracks in monkey Y and all the tracks in monkey B were performed using the 120 ms epoch.

Segments of EMG activity associated with each stimulus were evaluated and accepted for averaging only when the average of all EMG data points over the entire epoch was ⩾5% of full-scale input level (±5 V) on our data acquisition system (Power 1401, Cambridge Electronic Design Ltd, Cambridge, UK). This prevented averaging segments where EMG activity was minimal or absent (McKiernan *et al.*, 1998). EMG recordings were tested for cross-talk by computing EMG-triggered averages. Muscles showing cross-talk of 15% or greater were eliminated from the database (Cheney and Fetz, 1980).

When no poststimulus effects were detected at 60 μA, repetitive intracortical microstimulation (R-ICMS) was applied to determine if a motor output representation could be identified for that site. Using this method, the representation of muscles not implanted with electrodes (face, trunk, and hindlimb) could also be identified. R-ICMS consisted of a train of 10 symmetrical biphasic stimulus pulses at a frequency of 330 Hz (Asanuma and Rosen, 1972) and an intensity of 30–100 μA. Evoked movements and muscle contractions detected visually and/or with palpation were noted. Mouth and hindlimb movements were evoked with ICMS in the most anterior and posterior track penetrations respectively. Tracks located >6 mm lateral to the midline did not show poststimulus effects. These results are in agreement with the SMA forelimb boundaries reported by others (He *et al.*, 1995; Luppino *et al.*, 1991).

Comparison data for M1 output effects was obtained from two monkeys using the data set collected by Park *et al.* (2004). The task conditions for both the SMA and M1 data were the same. Data published by Park *et al.* (2004) was restricted to layer V sites in M1. For comparison purposes, in this paper we have expanded the analysis of M1 data to include sites in all layers of the gray matter. The M1 data were collected using an epoch of 60 ms (20 ms pre-trigger to 40 ms after the trigger), a minimum of 500 trigger events, and a stimulus intensity of 15 μA on animals of comparable size.

Data Analysis

At each stimulation site, averages were obtained from all 24 muscles. Poststimulus facilitation (PStF) and suppression (PStS) effects were computer-measured as described in detail by Mewes and Cheney (1991). Non-stationary, ramping baseline activity was routinely subtracted from StTAs using custom analysis software. Mean baseline activity and standard deviation (SD) were measured from EMG activity in the pre-trigger period (20–30 ms). StTAs were considered to have a significant PStF if the envelope of the StTA crossed a level equivalent to 2 SD of the mean of the baseline EMG for a period of time ⩾1.25 ms (5 points). Peaks that did not exceed 2 SD for at least 1.25 ms were considered insignificant. The magnitude of PStF and PStS was expressed as the percent increase or decrease in EMG activity above (facilitation) or below (suppression) baseline (Cheney and Fetz, 1985; Kasser and Cheney, 1985; Cheney *et al.*, 1991).

Results

Poststimulus effects were obtained from all layers of the gray matter in the forelimb representation of the left SMA in two monkeys and the left M1 in two additional monkeys. StTA data were collected from a total of 397 sites in SMA of

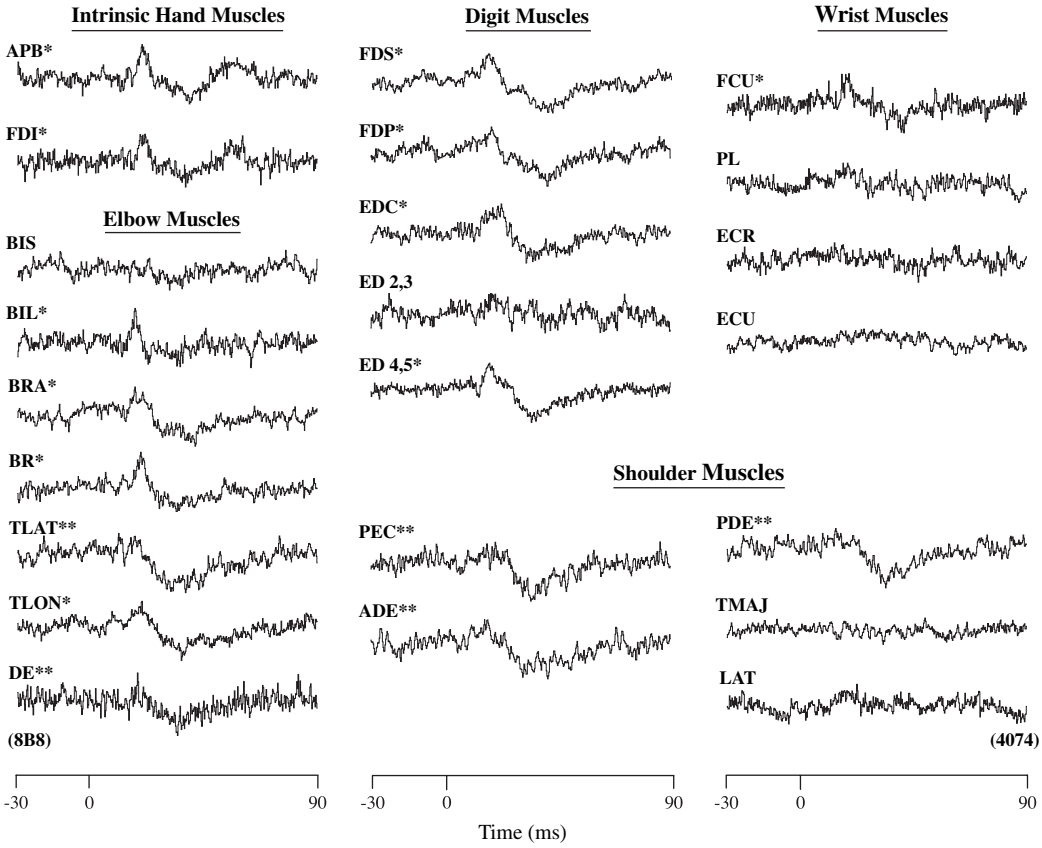

Figure 2. Poststimulus facilitation (PStF) and suppression (PStS) of forelimb muscles from one SMA site (8B8). Time zero on the horizontal axis corresponds to the stimulus event. Stimulation was 60 μA at 10 Hz. PStF effects were observed in both proximal (BIL, BRA, BR, TLON) and distal (APB, FDI, FDS, FDP, ED 4,5, EDC, FCU) forelimb muscles. Pure PStS effects were observed in proximal (ADE, PEC, PDE, TLAT, DE) forelimb muscles. Individual records were based on 3074–4074 trigger events. PStF effects are marked by a single asterisk and PStS effects by a double asterisk.

two monkeys at an intensity of 60 μA (Table 1). These sites yielded a total of 897 individual poststimulus effects, including 450 (54%) PStF effects and 385 (46%) PStS effects. M1 StTA data used for comparison to SMA were collected from two additional monkeys that were part of a previous study (Park *et al.*, 2004). These data were based on 3226 individual poststimulus effects, including 1971 (61%) PStF effects and 1255 (39%) PStS effects.

Figure 2 shows an example of poststimulus effects from one SMA site. This site was located in the mesial wall of SMA and is represented by an open circle on the brain surface map of monkey B (Fig. 1). At this site, significant PStF effects were observed in several proximal and distal muscles as indicated by asterisks. In some cases, PStF was followed by suppression (Fig. 2, ED 4,5). The suppression component of biphasic effects was not measured because of uncertainty about its origin and exact onset. PStS, separate from facilitation, was also present at this site, e.g. PDE.

Figure 3*A* shows the distribution of PStF and PStS onset latencies for effects obtained from SMA. The distribution for PStF was bimodal with an early peak containing onset latencies of <40 ms (384 effects, 85% of PStF) and a late peak with onset latencies of >40 ms (66 effects, 15% of PStF). Early PStF from SMA had a mean latency of 15.2 ± 4.5 ms compared with an onset latency of 9.7 ± 2.1 ms for M1 PStF effects (Table 2). Late PStF from SMA had a mean latency of 55.2 ± 7.2 ms. Examples of short and long latency PStF are illustrated in Figure 4. Long latency PStF typically occurred without early PStF (EDC), but in some cases it was preceded by short latency facilitation (BIS) or by PStS. M1 has yet to be tested for late effects using a long analysis epoch.

Figure 3*B* shows the distribution of onset latencies for PStS from SMA. The distribution was unimodal with mean onset latency of 32.4 ± 9.2 ms. In comparison, the mean latency of M1 PStS was 15.6 ± 4.4 ms. The distribution of PStF and PStS latencies for SMA effects were broader than M1 effects, as reflected in larger standard deviations (Table 2). Examples of PStS from SMA include PDE, ADE and PEC in Figure 2.

The latencies and magnitudes of PStF from SMA and M1 for muscles acting at different joints are given in Table 3. At all joints, SMA mean onset latencies were greater that those from M1 ($P < 0.001$, Mann–Whitney rank sum test). The onset latencies from SMA averaged 5.5 ms longer than those from M1. Statistical comparison of mean PStF onset latency from SMA for different joints revealed that digit muscle onset latency was significantly longer than shoulder and elbow muscle latencies ($P < 0.01$, Holm–Sidak method). In comparison, except for PStF in intrinsic hand muscles, distal muscle onset latencies from M1 sites were shorter than proximal muscle onset latencies ($P < 0.001$, Holm–Sidak method). Proximal muscle PStF had the shortest onset latency from SMA whereas the distal muscle PStF had the shortest onset latency from M1.

Table 3 also gives the average magnitude of PStF for muscles acting at different joints. The average magnitudes of PStF from

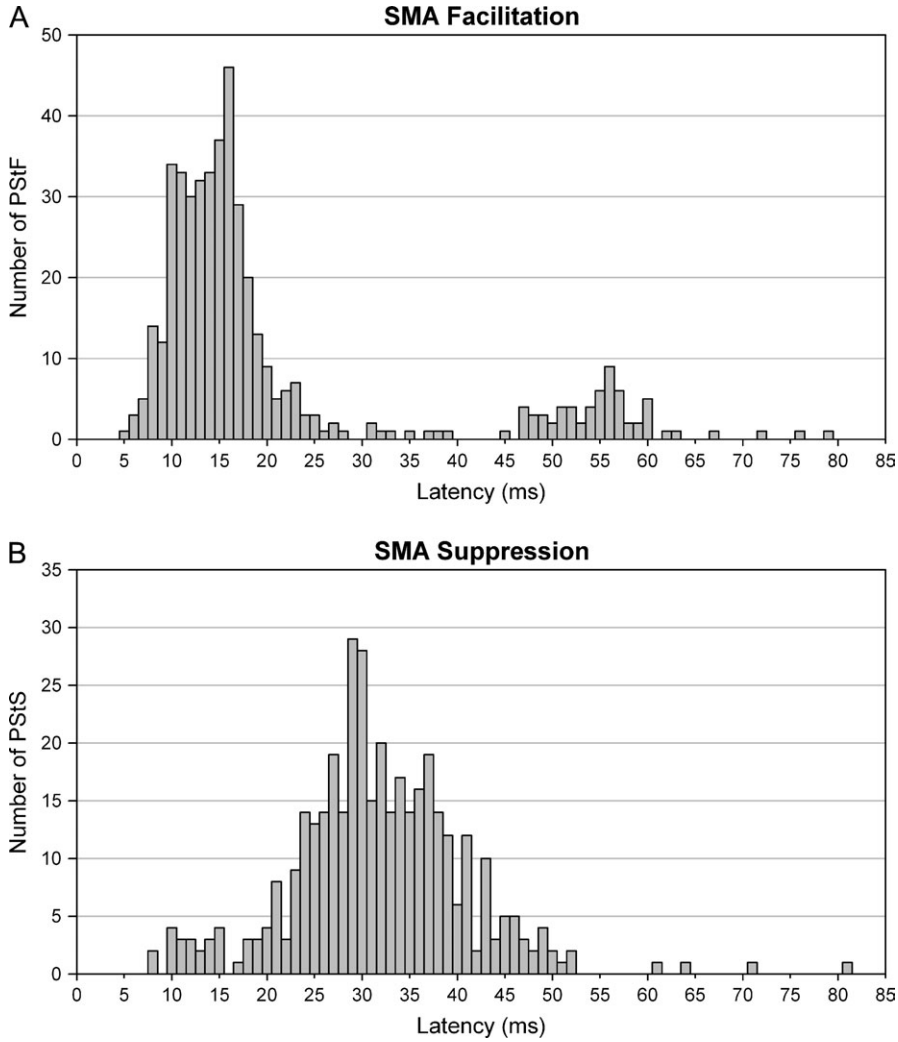

Figure 3. (*A*) Distribution of SMA PStF onset latencies for muscles at all forelimb joints ($n = 450$). (*B*) Distribution of PStS onset latencies for muscles at all forelimb joints ($n = 385$).

Table 1
Summary and comparison of data collected from SMA

	SMA			M1 total
	Monkey B	Monkey Y	Total	
Electrode tracks	21	22	43	248
Sites stimulated	170 (43%)	227 (57%)	397	2,477
StTA records	4,048	5,448	9,496	59,448
PStF effects (latency < 40 ms)	103	281	384 (46%)	1,971 (61%)
PStF effects (latency > 40 ms)	38	28	66 (8%)	NT
PStS effects	242	143	385 (46%)	1,255 (39%)
Total PStF and PStS effects	383	452	835	3,226

SMA, supplementary motor area; M1, primary motor cortex; StTA, stimulus triggered average; PStF, poststimulus facilitation; PStS, poststimulus suppression; NT, not tested. M1 data were from a previously study some of which has been published (Park *et al.*, 2004). M1 and SMA data came from different monkeys.

SMA were all statistically weaker than effects from M1 in the corresponding joints ($P < 0.001$, Mann–Whitney rank sum test). The magnitude of PStF from M1 sites was substantially greater for distal muscles compared with that of proximal muscles, and there was a trend toward a progressive increase in magnitude the more distal the group of muscles. This difference was not evident in the data for SMA. In fact, the only significant differences that emerged in the data for SMA was that the magnitude of PStF from intrinsic hand muscles was weaker than that from elbow and wrist muscles ($P < 0.05$, Holm–Sidak method) and shoulder muscle PStF was weaker than that from elbow, wrist, and digit muscles ($P < 0.001$, Holm–Sidak method).

Figure 5 shows the distribution of PStF and PStS magnitudes for effects obtained from SMA. The average magnitudes of the PStF (early onset) and PStS from SMA at 60 μA expressed as peak-percent-increase (ppi) or decrease (ppd) relative to baseline were 13.8 ± 6.2 and –11.9 ± 4.1%, respectively. Late onset PStF from SMA had an average magnitude of 11.3 ± 4.2%. In comparison, the magnitudes of PStF and PStS from sites in M1 at 15 μA were 50.2 ± 63.5 and –23.8 ± 8.8%, respectively (Table 2). In previous work (Widener, 1989), we showed that the relationship between stimulus intensity applied to M1 cortex and ppi measured from spike triggered averages is linear. Accordingly, we performed a linear extrapolation of this relationship to estimate the magnitude of M1 PStF and PStS at 60 μA for more direct comparison to SMA magnitudes. M1 PStF magnitude extrapolated to 60 μA was 206.1%; M1 PStS magnitude was –97.7%. The extrapolation was based on data for stimulus sites in all cortical layers.

Table 2
Comparison of the latency and magnitude of SMA and M1

	Early PStF (onset latency < 40 ms)		Late PStF (onset latency > 40 ms)		PStS, all latencies	
	Onset latency (ms)	Magnitude (peak % increase)	Onset latency (ms)	Magnitude (peak % increase)	Onset latency (ms)	Magnitude (peak % decrease)
SMA (60 μA)	15.2 ± 4.5	13.8 ± 6.2	55.2 ± 7.2	11.3 ± 4.2	32.4 ± 9.2	−11.9 ± 4.1
MI (15 μA)	9.7 ± 2.1	50.2 ± 63.5	NT	NT	15.6 ± 4.4	−23.8 ± 8.8
MI (60 μA) extrapolated	—	206.1	—	—	—	−97.7

NT, not tested; M1, primary motor cortex; SMA, supplementary motor area. Magnitude is the peak increase or decrease expressed as a percentage of the baseline. M1 data are from a previously collected data set (Park *et al.*, 2004) reanalyzed to include sites in all cortical layers. Extrapolation of M1 magnitudes to 60 μA is based on the work of Widener (1989) showing a linear relationship between stimulus intensity and the magnitude of PStF. Extrapolation of PStS was also based on a linear relationship.

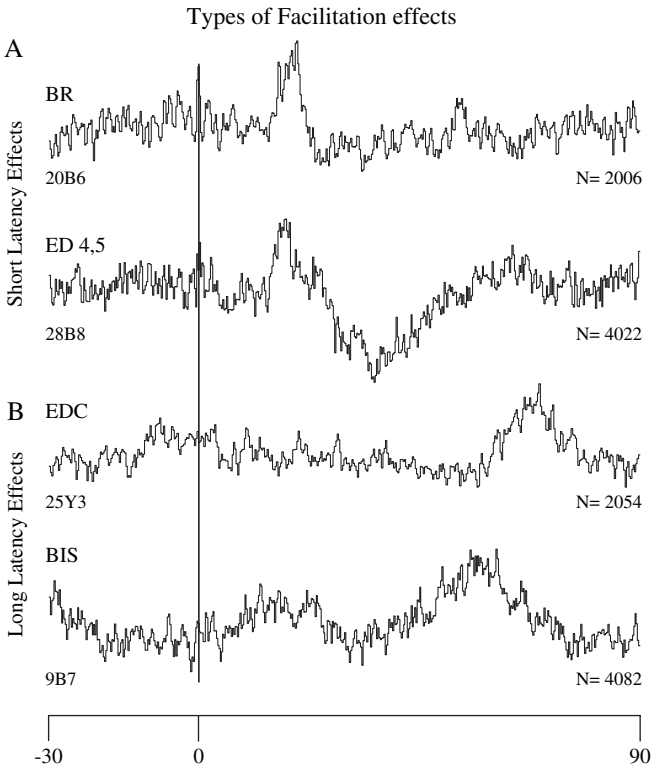

Figure 4. Types of facilitation effects observed in stimulus triggered averages of EMG activity from sites in SMA. (*A*) Short latency effects. (*B*) Long latency effects. Time zero corresponds to the stimulus event. N, number of trigger events. Muscle abbreviations given in text.

Discussion

The goal of this paper was to analyze the magnitude and latency of effects from SMA to 24 muscles of the forelimb in rhesus macaques and compare these effects with those from M1. Our results show that StTA effects from SMA have longer onset latencies and are much weaker than those from M1. In addition, unlike M1, effects in distal muscles from SMA are not stronger than those in proximal muscles. The results also demonstrate a bimodal distribution of PStF onset latencies from SMA with clearly early and late effects. Early SMA effects had a mean onset latency that was 5.5 ms longer than the mean onset latency of PStF from M1. SMA onset latencies also exhibited greater variability than those from M1. The latency of poststimulus effects in stimulus triggered averages of EMG activity reflects a combination of conduction distance, conduction velocity, and synaptic transmission in the anatomical pathway from the stimulation site to the muscle. The longer latency and greater variability in latency of SMA effects may reflect a more indirect coupling to motoneurons and slower corticospinal conduction velocity than exists for M1 (Palmer *et al.*, 1981; Macpherson *et al.*, 1982; Maier *et al.*, 2002). In fact, SMA has only limited corticospinal projections to motor nuclei of the ventral horn: 11% in the cervical and upper thoracic segments compared with 28% for M1 (Dum and Strick, 1996). The majority of corticospinal terminations from SMA (87%) are confined to the intermediate zone of the spinal cord (laminae V–VIII), where different populations of interneurons are located (Dum and Strick, 1996). This suggests that a major contribution of SMA to movement initiation and control is through its innervation of spinal interneurons influencing reflex and other spinal circuits rather than providing direct monosynaptic input to the motoneurons. This view is supported by the findings of the current study in which the

Table 3
Comparison of the latency and magnitude of PStF from sites in SMA and M1 per joints

	SMA			M1		
Joint	No. of effects	Onset latency (ms)	Magnitude %	No. of effects	Onset latency (ms)	Magnitude %
Shoulder	68	14 ± 4.9	10.5 ± 4.8	230	9.9 ± 2.5	23.7 ± 10.5
Elbow	103	14.7 ± 4.1	14.8 ± 6.4	561	9.9 ± 2.2	31.9 ± 20.8
Wrist	85	15.3 ± 3.7	15.4 ± 5.4	500	9.3 ± 2.1	60.8 ± 74.6
Digit	102	16.3 ± 5.2	14.1 ± 5.7	477	9.3 ± 1.9	65.6 ± 85.8
Intrinsic hand	26	15.7 ± 4.5	12.2 ± 9.4	203	10.4 ± 1.3	68.3 ± 63.2

Values are means and magnitudes ± SD. Data are based on early PStF (onset latency < 40 ms). Stimulation at 60 μA for SMA and 15 μA for M1. % = peak percent increase above baseline. M1 date are from a previously collected data set (Park *et al.*, 2004) reanalyzed to include sites in all cortical layers. Average onset latencies and magnitudes of PStF from SMA were all statistically different from corresponding M1 latencies and magnitudes ($P < 0.001$, Mann–Whitney rank sum test). The mean onset latencies and magnitudes of PStF from SMA and M1 showed the following statistically significant differences. Onset latency differences ($P < 0.01$, Holm–Sidak method): SMA, digit versus shoulder and elbow; M1, all were different except digit versus wrist, and shoulder versus elbow. Magnitude differences ($P < 0.05$, Holm–Sidak method): SMA, shoulder versus digit, wrist and elbow, and intrinsic versus wrist and elbow muscles; M1, all were different except digit versus wrist and intrinsic hand.

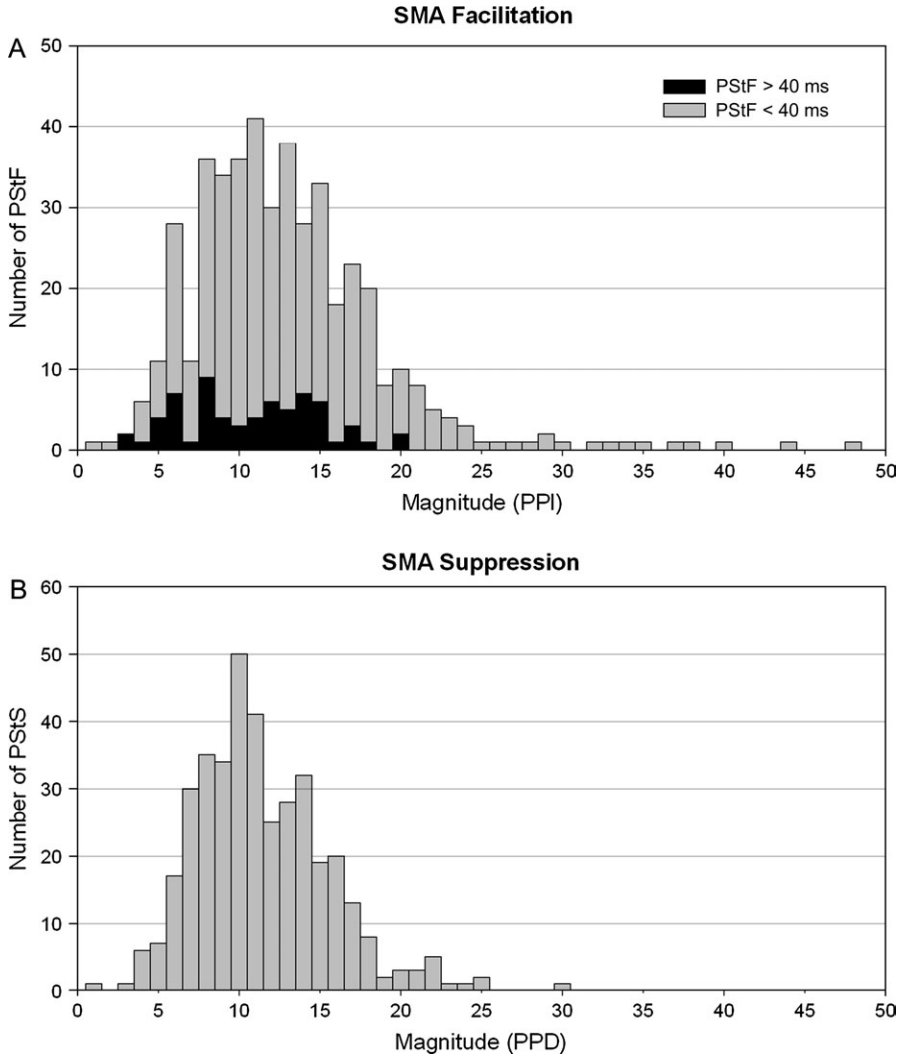

Figure 5. (*A*) Distribution of SMA PStF magnitudes for muscles at all forelimb joints ($n = 450$). Black shading indicates long latency PStF (>40 ms) effects. Light shading indicates short latency PStF (<40 ms) effects. The magnitudes are expressed as peak percent increase (ppi) above baseline. (*B*) Distribution of SMA PStS magnitudes for muscles at all forelimb joints ($n = 385$). Magnitudes are expressed as peak percent decrease (ppd) below baseline.

magnitudes of PStF and PStS from SMA were vastly weaker than those from M1 and the onset latencies of PStF at all joints were substantially greater than for M1. This conclusion is also supported by the work of Maier *et al.* (2002) showing that the area of densest labeling from M1 in lamina IX motor nuclei supplying the hand muscles was ~13 times the area of labeling from SMA.

As mentioned above, corticospinal neurons in SMA are smaller and have slower conduction velocities compared with M1 corticospinal neurons. Corticospinal neurons in SMA have velocities ranging from 20 to 63 m/s (Palmer *et al.*, 1981; Macpherson *et al.*, 1982; Maier *et al.*, 2002). Using 63 m/s as the fastest conducting SMA corticospinal neurons, we estimated that PStF effects with a latency of ⩽7.5 ms should be monosynaptic. In arriving at this estimate, we used times for synaptic delay, stimulus activation of corticospinal neurons and peripheral conduction based on previous reports (Fetz and Cheney, 1980; Cheney and Fetz, 1985). Using ⩽7.5 ms as the latency criterion for a monosynaptic effect, 1.7% of the PStF effects we recorded from SMA would be monosynaptic. This result is consistent with the sparse projections to motor nuclei reported by Maier *et al.* (2002).

SMA's primary contribution to the control of movements might be achieved largely indirectly through its projections to M1 (Muakkassa and Strick, 1979). Tokuno and Nambu (2000) showed that stimulation of SMA evoked excitatory responses in 64% of the M1 pyramidal tract neurons tested. The mean latency of these responses was 4.3 ms. In our data, this is similar to the difference in mean latency of PStF from SMA compared with that from M1 of 5.5 ms (longer for SMA), and consistent with a potential role of M1 in mediating SMA effects. While direct excitation of M1 corticospinal neurons is clearly a possibility, during volitional movement, SMA might also enhance M1 corticospinal output associated with other inputs (Cerri *et al.*, 2003). Tokuno and Nambu (2000) also showed that 31% of the responses in M1 pyramidal tract neurons evoked by stimulation of SMA were pure inhibitory responses with a mean latency of 6.7 ms. Our PStS effects had latencies that averaged 16.8 ms longer than M1 PStS effects. While this latency difference is also compatible with the possibility that these effects might be mediated through M1, it is greater than would be expected for a simple relay in which M1 corticospinal neurons with inhibitory muscle effects are facilitated by SMA or

M1 neurons with excitatory effects are suppressed. The mechanism of late PStF from SMA is unclear. The latency seems too long to be consistent with a relay through M1. In some cases, late PStF is preceded by suppression suggesting post-inhibitory rebound mechanism. However, late PStF was typically observed without any preceding PStS or early PStF in the same record so post-inhibitory rebound is an unlikely mechanism.

Effects from M1 were stronger than those from SMA even though the M1 stimulus intensity was 15 μA, compared with 60 μA for SMA. Extrapolating the magnitudes of M1 PStF and PStS to 60 μA yielded facilitation and suppression effects from M1 that were vastly stronger (15- and 8-fold respectively) than those from SMA. These results again support the recent findings of Maier *et al.* (2002) showing that while both SMA and M1 evoke corticomotoneuronal EPSPs in forelimb motoneurons, those from M1 are far more numerous and much stronger than those from SMA.

We conclude that the corticospinal connections from SMA provide relatively weak direct input to spinal motoneurons compared with the robust effects from M1. The effects from SMA might be predominantly achieved indirectly. Innervation of interneurons in the intermediate zone of the spinal cord and/or projections to M1 might be the primary mechanisms by which SMA influences motoneurons.

Notes

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