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Motor Outputs From the Primate Reticular Formation to Shoulder Muscles as Revealed by Stimulus-Triggered Averaging

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Abstract

The motor output of the medial pontomedullary reticular formation (mPMRF) was investigated using stimulus-triggered averaging (StimulusTA) of EMG responses from proximal arm and shoulder muscles in awake, behaving monkeys (*M. fascicularis*). Muscles studied on the side ipsilateral (i) to stimulation were biceps (iBic), triceps (iTri), anterior deltoid (iADlt), posterior deltoid (iPDlt), and latissimus dorsi (iLat). The upper and middle trapezius were studied on the ipsilateral and contralateral (c) side (iUTr, cUTr, iMTr, cMTr). Of 133 sites tested, 97 (73%) produced a poststimulus effect (PStE) in one or more muscles; on average, 38% of the sampled muscles responded per effective site. For responses that were observed in the arm and shoulder, poststimulus facilitation (PStF) was prevalent for the flexors, iBic (8 responses, 100% PStF) and iADlt (13 responses, 77% PStF), and poststimulus suppression (PStS) was prevalent for the extensors, iTri (22 responses, 96% PStS) and iLat (16 responses, 81% PStS). For trapezius muscles, PStS of upper trapezius (iUTr, 49 responses, 73% PStS) and PStF of middle trapezius (iMTr, 22 responses, 64% PStF) were prevalent ipsilaterally, and PStS of middle trapezius (cMTr, 6 responses, 67% PStS) and PStF of upper trapezius (cUTr, 46 responses, 83% PStS) were prevalent contralaterally. Onset latencies were significantly earlier for PStF (7.0 ± 2.2 ms) than for PStS (8.6 ± 2.0 ms). At several sites, extremely strong PStF was evoked in iUTr, even though PStS was most common for this muscle. The anatomical antagonists iBic/iTri were affected reciprocally when both responded. The bilateral muscle pair iUTr/cUTr demonstrated various combinations of effects, but cUTr PStF with iUTr PStS was prevalent. Overall, the results are consistent with data from the cat and show that outputs from the mPMRF can facilitate or suppress activity in muscles involved in reaching; responses that would contribute to flexion of the ipsilateral arm were prevalent.

INTRODUCTION

The reticulospinal tract is one of the 4 major descending motor systems, but understanding of this system is limited. Early experiments in the medial pontomedullary reticular formation (mPMRF) of the cat reported that stimulation of the rostradorsal region facilitated cortically evoked facilitation of muscle tone, but stimulation of the caudoventral region suppressed cortically evoked facilitation, suppressed segmental reflexes, and eliminated decerebrate rigidity (Magoun and Rhines 1946; Rhines and Magoun 1946). Sprague and Chambers (1954) later demonstrated that these global effects were elicited only by prolonged, intense stimulation. With stimulus current levels just above threshold, Sprague and Chambers revealed more complex reticulospinal actions. The most common response observed was a combination

of ipsilateral forelimb flexion, contralateral forelimb extension, and turning of the head to the stimulated side. In some cases, movement was limited to a single body segment (forelimb, head, or hindlimb). Thus Sprague and Chambers found that outputs from the mPMRF can be more specific than those described by Magoun and Rhines.

As a descending system, the reticulospinal tracts are remarkable for the potential of individual neurons to have widespread effects. Projections from the mPMRF descend throughout the length of the spinal cord in the medial and lateral regions of the ventral funiculus (Kuypers 1981). Terminals from single reticulospinal axons project to both sides of the spinal cord at multiple segmental levels (Kuypers 1981; Matsuyama et al. 1997, 1999; Peterson et al. 1975; Sasaki 1997) and are concentrated in the ventromedial gray, but also reach the lateral horn and motoneurons of the neck and forelimb (Alstermark et al. 1987; Holstege and Kuypers 1987; Iwamoto et al. 1990; Sasaki 1999). Electrophysiological methods have revealed excitatory monosynaptic projections to motoneurons of neck and axial muscles from the dorsocaudal and ventrostral regions of the mPMRF (Peterson 1979; Peterson et al. 1975, 1979). Stimulation in the ventrostral region has also produced monosynaptic excitation of flexor and extensor motoneurons, whereas polysynaptic excitation and inhibition were produced in the same motoneurons from the dorsocaudal regions (Peterson 1979; Peterson et al. 1979). Inhibitory effects appear to rely on spinal interneurons (Takakusaki et al. 2001), and contralateral effects likely depend on commissural interneurons as well as direct projections (Jankowska et al. 2003).

In intact, awake cats, Drew and Rossignol (1990a) reported that repetitive microstimulation produced movement patterns that most often included flexion of the ipsilateral limb, extension of the contralateral limb, and turning of the head to the ipsilateral side. These results were consistent with the findings of Sprague and Chambers (1954), except Drew and Rossignol (1990a) did not observe exclusive movement of a single body segment. Drew's work has demonstrated a central role for the reticulospinal system in the control of locomotion in the cat (Drew 1991; Drew et al. 1986; Matsuyama et al. 2004), as well as postural support for reaching movements from a tripod stance (Schepens and Drew 2003a). This functional role is consistent with the anatomical and physiological evidence described above, indicating that reticulospinal outputs can simultaneously affect axial muscles and proximal limb muscles in the forelimb and hindlimb.

Existing data from the primate indicates that, as in the cat, some reticulospinal projections are monosynaptic (Shapovalov 1972). Reticulomotoneuronal projections, however, are less prevalent than corticomotoneuronal projections, and terminate mostly in laminae VII and VIII, instead of lamina IX. In the awake monkey, stimulation within and around nucleus reticularis gigantocellularis (NRGc) has produced head movement, as well as movement of the face, mouth, neck, shoulder, and arm (Cowie and Robinson 1994). These findings were based solely on observation without EMG, and the effects for individual stimulus sites were not reported.

In the primate, the majority of cortical input to the mPMRF originates in the premotor cortex, supplementary motor area, and primary motor cortex (Keizer and Kuypers 1989). Considering the critical roles of these areas for the planning, preparation, and execution of reaching (Tanji 2001; Wise et al. 1997), one might expect the reticulospinal system to play an important role in voluntary reaching. Such a role is supported by the presence of movement related discharge in mPMRF neurons during reaching for the primate (Buford 1996) and the cat (Schepens and Drew 2003b). Areas of the mesencephalic reticular formation that project to the mPMRF have also been shown to have neural activity related to reaching (Gibson et al. 1998; Werner et al. 1997). To begin to describe the role of the reticulospinal system for the control of voluntary reaching movements in the primate, the present study used the method of stimulus-triggered averaging (StimulusTA) to characterize the sign and distribution of mPMRF outputs to axial,

shoulder, and proximal arm muscles (Cheney and Fetz 1985). Portions of these results were previously presented in abstracts (Davidson and Buford 2001, 2002).

METHODS

Subjects, task, and surgery

The subjects were 2 male *Macaca fascicularis* monkeys (C and D) trained for a separate study. In the context of an instructed delay task, the subjects performed planar reaching movements (5.08-cm displacement) from a central position to one of 4 peripheral targets (45, 135, 225, and 315° in Cartesian coordinates). A sip of flavored applesauce was the reward for each correct trial. The head was restrained for recording and stimulation to help maintain stable electrode positioning. Experimental procedures were approved by the ILACUC of The Ohio State University, and subject care was according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

After training, a stainless steel recording chamber was implanted over a craniotomy in the left parietal bone. The chamber's axis was in the frontal plane, angled 10° to the left from the parasagittal plane to allow access to the right mPMRF, and aimed for stereotaxic coordinates AP0, ML0, DV-12 (Horsley–Clark stereotaxic coordinates, Szabo and Cowan 1984). Surgery was performed under isoflurane inhalation anesthesia with ketamine HCl as a preanesthetic. Analgesics (buprenorphine, ibuprofen) and a long-acting antibiotic (Baytril) were given after surgery.

EMG implants

Electromyographic data were collected with acute percutaneous (first 6 averages from subject D) and chronically implanted pairs of Teflon-coated stainless steel wires. Wire pairs were separated by approximately 5 mm and inserted into the muscle by a hypodermic needle (Betts et al. 1976; Park et al. 2000). For the chronic implants, the wires were led subcutaneously to a 17-pin plug (WPI #223-1617) mounted in the dental acrylic of the cranial implant. The integrity of EMG implants was verified by stimulating through the EMG wires, and by periodic testing of electrode impedances. Because recordings were made from the right reticular formation, ipsilateral muscles were located on the right side. For both subjects, electrodes were located in the contralateral and ipsilateral upper trapezius (cUTr, iUTr) and ipsilateral posterior deltoid (iPDlt). Additional implants in subject C were located on the ipsilateral side in latissimus dorsi (iLat), long head of triceps (iTri), long head of biceps (iBic), and in contralateral middle trapezius (cMTr). For subject D, additional implants were located in the ipsilateral anterior deltoid (iADlt) and ipsilateral middle trapezius (iMTr). EMG data for ipsilateral iBic and iTri were available from subject D for the 6 experiments conducted with percutaneous EMG. Over the 8 mo of study most EMG implants remained stable, except for iADlt in subject D, which failed in the last month.

EMG records were tested for the presence of cross talk between muscles. For this analysis, data were recorded for extended periods of time without stimulation. For these data files, motor unit action potentials from each muscle were selected as triggers for compiling EMG triggered averages for the remaining muscles. Cross talk was considered to be present if the EMG triggered averaged of any muscle exceeded 15% of the averaged amplitude of the triggering muscle (Cheney and Fetz 1985; Fetz and Cheney 1980). Overall, one data file from each week of the study was examined for each subject. Cross talk was discovered from the outset between the chronic recordings of iPDlt and iUTr in subject D, and as a result, iPDlt data were removed for that subject. No other cases of cross talk were observed.

Recording and stimulation

Extracellular recording and stimulation were performed with tungsten microelectrodes (0.2-mm stock) that were epoxy and polyimide insulated (Frederick Haer, Bowdoinham, ME). The electrode tips were conditioned with gold plating to produce recording impedances in the range of 90–200 k Ω . Electrodes were inserted through a thin-walled 23-gauge stainless steel guide cannula positioned in the recording chamber by an X–Y grid, and lowered into the brain stem with a manual hydraulic microdrive.

All recording and stimulation sites were in the right mPMRF (Fig. 2). The dorsal boundary of the recording/stimulating region was the abducens nucleus (defined by cells with firing rates proportional to eye abduction) (Luschei and Fuchs 1972); the ventral boundaries were the inferior olive and pyramidal tract. The facial nucleus defined the lateral boundary, and the medial boundary was located 0.5 mm lateral to the midline. Arm-related neurons were identified by their modulation of firing during arm movement and by their responses to manipulation of the arm and shoulder. Neuronal activity, EMG (sampled at 4.63 KHz), records of stimulation, hand position, and logic signals representing the state of the task were recorded with Spike2 software and a Power1401 acquisition unit (CED, Cambridge, UK). Neural data collected here were used as part of a separate study of the mPMRF activity during reaching (Buford 2000). After a recording track was complete, the electrode was retracted and single-pulse microstimulation for StimulusTA was applied at or near sites where task related neurons had been recorded.

To determine the appropriate stimulus current for each site, threshold testing was conducted with repetitive microstimulation (12 biphasic pulses, negative, then positive, 200 μ s/phase, 333 Hz) with a current ranging from 10 to 50 μ A. Threshold was defined as the current at which a muscle twitch or slight movement was consistently observed. For StimulusTA, low-frequency single-pulse microstimulation (13.3 Hz, 75-ms interval, 2,000 stimuli) were initially applied at a current intensity of about 1½ times the threshold. If no response was observed during threshold testing, single-pulse current for StimulusTA was set at 30 μ A. This current was chosen as a constant to permit testing for suppressive effects that may not have been evident on observation. In some cases, the current used for single pulses produced overt muscle twitches and current was decreased in 5- μ A increments until overt muscle twitches were abolished. Nevertheless, low-intensity stimuli (10 μ A) sometimes produced overt (though slight) twitches at some sites, and these records were included. The vast majority of the data reported here was associated with current intensities that did not produce any overt contraction with a single pulse.

Averaging and analysis

EMG records were adjusted to remove DC offsets, rectified, and averaged off-line using a custom script for Spike2. Averages were compiled over an 80-ms epoch that was divided into a 20-ms pretrigger period and a 60-ms posttrigger period. Triggers for periods when EMG exceeded the maximum range of the amplifier (4.5 V) were excluded on a channel-by-channel basis. Consequently, the number of triggers in a single average varied for each muscle. Approximately 1,900 triggers were typically used for StimulusTA analysis.

Criteria for a poststimulus effect (PStE) were established relative to the mean and SD of a prestimulus baseline derived from the first 19 ms of each average, ending 1 ms before the stimulus to prevent stimulus artifact from corrupting the baseline period. Averaged EMG responses that differed from the mean of the prestimulus EMG baseline by ≥ 2 SD of the mean for ≥ 2 ms were considered candidates for analysis (Mewes and Cheney 1991). Onset and offset latencies were determined by the points of intersection between the EMG averages and the ± 2 SD thresholds. The amplitudes of the PStEs were quantified by the SD score of the peak

(SDPk), the *z*-score (number of SDs) of the peak displacement from baseline, as well as by the mean percentage change (MPC), the percentage difference of mean EMG activity of the PStE from the EMG baseline (Cheney and Fetz 1985; Cheney et al. 1991; Kasser and Cheney 1985).

By using H-reflex testing in biceps and collision tests for reticulospinal neurons from the cervical spinal cord in other subjects, we have estimated the earliest onset latency for biceps from the mPMRF to be 4.5 ms (J. A. Buford, unpublished results). Because more proximally located muscles (e.g., upper trapezius) were examined in the present study, 3.5 ms was chosen as the minimum acceptable onset latency for all muscles.

To examine the possibility that fluctuations in the EMG unrelated to the stimulus may have produced some of the PStEs, random triggered averages (RandomTA) were compiled for sites where poststimulus effects were obtained. Using a custom script for Spike2 (CED), 2,000 fake stimulus events were created at random times within the period of stimulation and used as triggers for averaging. RandomTAs were computed and analyzed with procedures identical to those used for Stimulus TA.

There were 420 potentially significant events from StimulusTA, and 151 from RandomTA. Examination of the distributions indicated that events beginning after 25 ms were just as likely from RandomTA as they were from StimulusTA. The largest difference was present for onset latencies between 3.5 and 12.5 ms, where events from StimulusTA were 8 times more frequent than those from RandomTA. This was also a realistic time range for poststimulus effects to begin. Therefore we sought to develop additional criteria that would eliminate RandomTA events from the 3.5- to 12.5-ms window while preserving StimulusTA events. The parameters that discriminated most effectively between StimulusTA and RandomTA events were duration and MPC. As described in the RESULTS, by limiting the analysis to events with onset latencies from 3.5 to 12.5 ms (as detected with the 2 SD threshold), a duration of ≥ 2.5 ms, and a mean amplitude of $\geq 6\%$ (MPC), we accepted 199 events from StimulusTA. Only 13 RandomTA events were not eliminated by these criteria.

A 2-way ANOVA by muscle and response type (facilitation or suppression) was used to compare effects on onset latency, duration, SDPk, and stimulus current level. The frequencies of poststimulus facilitation (PStF) and poststimulus suppression (PStS) were compared across muscles with a chi-squared analysis. The significance level was set to $P \leq 0.05$.

Anatomy and histology

Electrolytic lesions were made with 20 μ A for 20 s (DC anodal) in the final tracks at specific points of interest. After all lesions were made, subjects were deeply anesthetized with sodium pentobarbital and perfused transcardially with phosphate-buffered saline, followed by phosphate-buffered formalin. The brain was removed and soaked in neutral buffered formalin with 30% sucrose for cryoprotection. Frontal sections were cut at 40 μ m on a freezing microtome and every 4th section was mounted and stained with cresyl violet. The sections were scanned at 1,200 dots per inch and the anatomical reconstructions were completed in software. Structures in the brain stem were identified according to a stereotaxic atlas (Szabo and Cowan 1984) and a template atlas available on-line from the primate information center at the University of Washington (Bowden et al. 2003). The locations of EMG recording electrodes were verified by post mortem dissection.

RESULTS

Task and EMG

A representative sample of EMG recorded from Monkey C during task performance is presented in Fig. 1. In this segment, the monkey began the trial by waiting in the start position, and then an instruction (target cue) was presented to direct movement to one of the 4 targets. The monkey was then given the movement cue and he subsequently moved to contact the correct target and held his hand on the target until the reward was given. After the reward, a new trial began. For the purpose of StimulusTA in the muscles studied, the task created moderate levels of EMG activity that were sufficient to allow observation of poststimulus facilitation or suppression. In iLat and the upper and middle trapezius muscles, EMG activity was often highest as the monkey held his hand in the start position. Modulation of iBic, iTri, and the deltoids was most evident during reaching to the targets.

Selected analyses were performed to determine whether the results of StimulusTA varied depending on the direction of movement. Stimulation sites chosen for this analysis included sites from which single pulse stimulation produced substantial PStEs for several muscles, and sites near cells that demonstrated a directional preference for at least one of the 4 targets. These records were chosen for this analysis because the potential of observing movement or target related variation in the responses were expected to be highest for these sites. In total, data from 10 sites (8%) were analyzed. In no case was there a substantial difference in the PStEs when triggers were separated on the basis of movement direction. There was also no substantial difference in the averages constructed from within the movement periods and the averages constructed from the overall period of stimulation. Therefore only results from the overall period of stimulation are presented here.

Locations of stimulus sites

The locations of stimulus sites were anatomically reconstructed and plotted by muscle and type of response (PStF vs. PStS) to examine the organization of stimulus sites. No somatotopic organization was evident for any muscle or response type. Effective sites for each muscle were intermixed, and PStS and PStF were evoked from sites throughout the region studied. The locations of stimulus sites in subject D that were effective in producing poststimulus effects in iUTr are presented in Fig. 2. Stimulus sites for this muscle were chosen for this illustration because it was the most responsive of all the muscles studied, and every site tested included a recording of this muscle. In Fig. 2A, stimulus sites for a selected plane [anterior–posterior (AP), –1] are superimposed on a coronal section; circles represent sites that evoked PStF, triangles represent PStS, and dashes indicate sites from which no PStE was produced. For all locations, stimulus sites are illustrated in the parasagittal view in Fig. 2B, and in a frontal view in Fig. 2C. As the illustrations show, sites that produced PStF and PStS were intermixed.

Between the 2 subjects, stimulation was applied at 189 sites from 89 electrode penetrations. After the anatomical reconstruction, 56 sites were found to be outside the predetermined boundaries of the mPMRF (see METHODS) and were excluded. The lateral boundary of the acceptable zone was the medial edge of the facial nucleus. Stimulation at sites lateral to this resulted either in no movement whatsoever or in movement primarily of the face. Stimulation at sites that were too ventral produced no effect unless the electrode was so deep as to stimulate the corticospinal tract directly, resulting in brisk contralateral movements. Medial sites were excluded to prevent stimulation of the medial longitudinal fasciculus. Stimulation in sites that were too dorsal typically produced eye movements. This left 133 stimulation sites for the study. Of these, 109 (82%) were within 0.5 mm of a cell with task-related activity for the reaching task. The remaining 24 sites (18%) were within the same region of the mPMRF. Trains of stimuli (12 pulses at 333 Hz) within this zone produced muscle twitches in the arm, shoulder,

and trunk, and occasionally resulted in movement of the face, ear, and neck. The head was restrained, so it is not known whether head movement would have resulted from these stimulus sites. It is presumed that activation of muscles such as the upper trapezius could have moved the head, if it had been free.

Selection of poststimulus effects

Figure 3 illustrates the detection of PStEs using the ± 2 SD criterion. As illustrated, sequential events with the same or opposite sign could be observed in the response of a single muscle. In this example, cUTr PStF was followed by 2 periods of PStS. Because of the possibility that the second and third events may have resulted from segmental effects that were a consequence of the initial output, the present analyses were limited to the first PStE for each muscle. Accordingly, the PStEs analyzed for the StimulusTA presented in Fig. 3 included only 2 events: PStF in cUTr and PStS in iUTr. There were periods when the poststimulus waveforms of iADlt and iMTR crossed the 2 SD threshold, but these responses and others like them did not meet the 2.5-ms minimum duration or the 6% minimum value for MPC.

The distributions of onset latencies for RandomTA and StimulusTA (Fig. 4A) were compared with a uniform distribution with a one-sample Kolmogorov–Smirnov test. The distribution for StimulusTA was significantly different from a uniform distribution ($P < 0.000$), but the RandomTA distribution was not ($P = 0.399$). Events with onsets at long latencies were suspect because they could have resulted from indirect routes, such as the gamma loop, through mechanisms like those proposed by Kasser and Cheney (1985). To determine a cutoff latency beyond which StimulusTA data would not be analyzed, the mean and SD of the number of events per 2-ms bin for the RandomTA data were calculated. On average, there were 2.5 ± 2.0 RandomTA events per 2-ms bin. Taking 2 SD over the mean as a cutoff (dashed horizontal line, Fig. 4A), it was evident that events with onset latencies of 26–28 ms (represented by the bar at 28 ms) or greater could not be accepted because they were most likely a result of random fluctuations in the levels of EMG. Further, most PStEs with onsets in the first 25 ms actually occurred within the first 12.5 ms. PStEs with onset latencies between 12.5 and 25 ms were 25% as common in the StimulusTA data set as in the RandomTA data set. PStEs with onsets between 3.5 and 12.5 ms, however, were 15 times more likely for StimulusTA than for RandomTA, so $< 7\%$ of the earlier PStEs were likely to be attributable to chance. Consequently, all remaining analyses were limited to PStEs with onsets between 3.5 and 12.5 ms. This early window included 199 PStEs, of which 105 (53%) were PStS and 94 (47%) were PStF.

Stimulus currents and magnitudes of poststimulus effects

Stimulus currents for StimulusTA ranged from 10 to 50 μA , and the average current for all sites was $31 \pm 7 \mu\text{A}$. Because response amplitude was a primary criterion for selection of significant PStEs and the stimulus level varied for single-pulse stimulation, it was important to determine whether differences in PStE amplitudes could be explained by the use of different stimulation currents. For all events detected, neither an ANOVA of response magnitude by current [$F_{(7,418)} = 1.03$, $P = 0.41$] nor a regression of current against response magnitude ($r^2 = 0.004$, $P = 0.10$) showed any significant relationship between these 2 variables. Thus variations in stimulus amplitude did not explain variations in response amplitude.

Figure 4B illustrates the distribution of response amplitudes in terms of the variable MPC. For PStEs accepted in the 3.5- to 12.5-ms window, MPC values ranged from 6 to 31% ($12.7 \pm 4.8\%$) for PStS, and from 6 to 1,296% ($41.5 \pm 142.7\%$) for PStF. The SDPk values ranged from 2.9 to 13.7 (mean 5.8 ± 2.1) for PStS and from 3.0 to 1176.9 (mean 47.6 ± 174.6) for PStF. Because there was a small number of PStF events with very large amplitudes, the medians of the MPC (13.1% PStF, 12.2% PStS) and SDPk (6.0 for PStF, 5.1 for PStS) values may be more

reliable indicators of central tendency for these measurements. For the medians, there was little difference between the average amplitude of PStF and PStS.

Latency and duration of poststimulus events

Average onset latency was significantly earlier for PStF (6.99 ± 2.21 ms) than for PStS ($8.58 \text{ ms} \pm 2.04$ ms), as indicated by the ANOVA [$F_{(1,182)} = 5.736$, $P = 0.018$]. PStF onset was sooner for 6 of the 9 muscles, and for iMTr and iUTr this difference was significant (Table 1). Although average onset latencies were earlier for PStS than for PStF in iTri, iLat, and iADlt, these differences were not significant. There was no significant difference found overall for the duration of PStS versus PStF. iUTr responses were significantly longer than those from all other muscles except iBic, iTri, and iLat. The average duration was longer for PStF than for PStS in iUTr, which was the only muscle to show a significant difference in duration by response type.

Effectiveness of stimulation and proportions of facilitation and suppression

The distributions of onset latencies for all PStF and PStS events with onsets between 3.5 and 25 ms are presented in Fig. 5 for each muscle. As in Fig. 4, each muscle was most likely to respond in the 3.5- to 12.5-ms interval; data after 12.5 ms are shown for informational purposes, only. Of the 133 sites analyzed, single-pulse stimulation at 97 (73%) produced a minimum of one PStE (PStF or PStS) for at least one muscle. Because the number of muscles available for recording was not always the same for each subject or electrode penetration, the percentage of muscles demonstrating a PStE was calculated as a fraction of the total number of muscles recorded for each stimulus site. On average, 38% of the muscles recorded demonstrated a PStE for each site tested.

The effectiveness of stimulation for each muscle was quantified as the percentage of sites where a PStE was observed for that muscle as a fraction of the number of stimulation sites for which that muscle's EMG was recorded (Fig. 5). The most commonly affected muscles were iUTr, cUTr, iTri, and iADlt, which responded to stimulation at 35–37% of the sites for which they were tested. The least commonly affected muscles were iBic (13%) and cMTr (11%). iPDlt and iLat responded for 27–28% of the sites for which they were tested.

As shown in Fig. 6, there were different proportions of PStF and PStS for most muscles studied ($\chi^2 = 64.1$, $P < 0.001$). PStF was the most frequent response for the elbow flexor, iBic (100%), and the shoulder flexor, iADlt (77%). PStS was most frequent for the elbow extensor, iTri (96%), and for the extensor/adductor of the humerus, iLat (81%). The frequencies of PStF and PStS were similar in the shoulder extensor iPDlt (59% PStS). Overall, for the arm and shoulder muscles, flexors demonstrated higher proportions of PStF and extensors demonstrated higher proportions of PStS. In the upper trapezius, an upward rotator and elevator of the scapula, 74% of ipsilateral events (iUTr) were PStS, whereas 78% of contralateral (cUTr) events were PStF. For the middle trapezius muscle, a scapular retractor, PStF, was more prevalent ipsilaterally (iMTr, 64%), and PStS was more prevalent contralaterally (cMTr, 67%).

Representative poststimulus effects

An example of a typical StimulusTA is presented in Fig. 7. In this example, the majority of the muscles sampled (5/7) demonstrated a PStE, each of which was consistent with the prevalent response for that muscle. PStF was present in iBic and cUTr, and PStS was present in iUTr, iTri, and iLat (see legend for response magnitudes). iPDlt and cMTr did not respond for this stimulus site. In Fig. 8A, iTri, iPDlt, iLat, and iUTr responded with PStS, their most prevalent sign of response. Figure 8B, however, shows PStS in cUTr and iMTr, which were usually facilitated, as well as the typical responses of PStF in iBic and iADlt. Thus outputs from the mPMRF demonstrated a variety of patterns.

Although PStS was the most prevalent response for iUTr, PStF events with very large amplitudes were sometimes observed for this muscle. In 8 cases, the magnitude of PStF in iUTr exceeded 48 SDPk; 5 ranged from 430 to 1177, with onset latencies between 4.4 and 8.3 ms. Stimulus currents for these 8 sites were consistent with those for other sites and ranged from 10 to 30 μ A. Even with a single pulse at 10 μ A, EMG deflections (not artifact) were visible in the raw record for some of these low-threshold sites. An example of such a response is illustrated in Fig. 9. At 30 μ A, the SDPk of the iUTr PStF event reached 85, compared with the relatively weak responses observed in other muscles for this site. Although some strong, early-latency responses did occur in other muscles, they were consistent with their most prevalent response and did not exceed 40 SDPk (typically <20). Many of these occurred simultaneously with a large-magnitude, short-latency PStF event in iUTr. Sites that elicited these strong PStF responses in iUTr were found throughout the area studied; no unique location was apparent.

Responses among antagonist and bilateral muscle pairs

The arrangement of the EMG implants in subject C permitted analysis of interactions between the anatomical antagonists iBic and iTri at 38 sites. In 2 cases, both muscles responded to stimulation at a single site. Both of these were reciprocal, with PStF in iBic concurrent with PStS in iTri (Fig. 7). The bilateral muscle pair, cUTr and iUTr, was recorded simultaneously for all 133 sites tested. There were 22 cases where both muscles responded to stimulation at a given site, so that 37% of the iUTr responses were paired with a cUTr response. These bilateral responses included a variety of combinations. In 10 of the 22 cases, the bilateral responses were concurrent. The most frequent type of concurrent response, present in 7 cases, was cUTr PStF concurrent with iUTr PStS, as illustrated in Fig. 10A. There were also 2 cases in which cUTr and iUTr were both facilitated, and all of these included strong PStF in iUTr (Fig. 9). In one case, both muscles were suppressed. In addition to concurrent responses, there were 10 serial responses, which were defined as cases in which the onset for one muscle came with ± 2 ms of the offset for the other (if a response fit the criteria for serial, it was not classified as concurrent). Eight of these serial responses included cUTr PStF followed by iUTr PStS, as illustrated in Fig. 10B. There were also 2 cases where bilateral PStS responses were serial.

DISCUSSION

In summary, StimulusTA of EMG was used in the context of a reaching task to characterize the motor output of the mPMRF in the monkey. The results are consistent with previous reports from the cat (Drew and Rossignol 1990a,b; Sprague and Chambers 1953, 1954), and indicate that the primate reticulospinal tract can facilitate or suppress muscles used for reaching. The ipsilateral arm most frequently responded with extensor suppression and flexor facilitation. In the trapezius, the most frequent ipsilateral responses were facilitation of middle trapezius and inhibition of upper trapezius, whereas the opposite pattern was observed contralaterally. Bilateral responses in the upper trapezius muscles were common, and most often this included PStS in iUTr and PStF in cUTr. The iUTr was unique in having a preponderance of responses that were PStS, but a small number of extremely large PStF responses. Onset latencies were shorter for PStF than for PStS.

Reliability of the results

In a study based on responses to electrical stimulation, it is important to be sure that stimulus intensities were appropriate to prevent excessive current spread. In the present study, currents ranged from 10 to 50 μ A, and the average current for all sites was 31 μ A, which was similar to current ranges used in comparable studies. Cowie and Robinson (1994) used 10- to 100- μ A stimulus trains (40 ms, 400 Hz) to study the output of the mPMRF for the control of head movements in rhesus monkeys, and effects were typically evoked with 40 μ A. For StimulusTA

of proximal arm and shoulder muscles from the magnocellular region of the primate red nucleus, Belhaj-Saif et al. (1998) used currents in the range of 20 μ A. In a StimulusTA study designed to map sites in the primary motor cortex with outputs to shoulder, elbow, wrist, and hand muscles, Park et al. (2001) used 15 μ A, increasing to 30 μ A only when 15 μ A was ineffective. In the reticular formation of the cat, Drew and Rossignol (1990a) estimated the effective spread of a 35- μ A stimulus train (33-ms train at 333 Hz) to be <0.5 mm. Because the stimuli for StimulusTA are single pulses, temporal summation should have been limited for the present study.

It is unlikely that the present results reflected the activation of structures outside of the mPMRF. Nevertheless, the potential for unintended activation of the corticospinal tract (CST) was a major concern for the present study. With single pulse and repetitive microstimulation, movement of the hand or fingers for the ipsilateral or contralateral side was never observed at any site studied, so it seems unlikely that the CST was directly activated. CST collaterals, however, do terminate in the mPMRF of the cat (Kably and Drew 1998; Keizer and Kuypers 1984) and monkey (Keizer and Kuypers 1989). Stimulation of CST collaterals could account for the present results if they excited root axons that projected exclusively to motoneurons or interneurons of proximal arm and shoulder muscles. A similar concern exists for the vestibular nuclei, which also project to the mPMRF (Bolton et al. 1992; Matsuyama and Drew 2000a,b; Wilson and Peterson 1981). This projection raises the possibility of indirect activation of the vestibular tracts as a consequence of mPMRF stimulation.

Shapovalov (1972) tested the hypothesis that CST collaterals were activated by mPMRF stimulation by recording lumbar α motoneuron responses to stimulation of the medial longitudinal fasciculus, NRGc, and nucleus reticularis pontis caudalis in pyramidotomized rhesus monkeys. In 38 subjects, the CST was interrupted by transection of the pyramids in the brain stem, by acute lesions of the spinal cord, or with unilateral or bilateral lesions of the precentral gyrus (allowing sufficient time for CST degeneration). Motoneuron responses to reticular formation stimulation for control subjects were similar to those of the pyramidotomized and cortically lesioned monkeys, and there was no evidence that the responses evoked from the reticular formation were a result of CST collateral stimulation. In a separate study performed by Shapovalov and colleagues (Shapovalov 1973), the ipsilateral lateral vestibular nucleus and the contralateral red nucleus were destroyed in the cat and lumbar α motoneurons responses to reticular formation stimulation were examined. From these experiments, the authors determined that the effects of mPMRF stimulation were not attributed to unintended activation of the lateral vestibulospinal tract (LVST) or the rubrospinal tract.

Overall, Shapovalov's findings suggest that the PStEs resulting from mPMRF stimulation in the present study were mediated by the reticulospinal tract and were not likely a consequence of unintended activation of the CST, the LVST, or their collaterals. These findings, however, do not disprove the argument that these structures were activated with single-pulse stimulation in the present study. It would be necessary to compare StimulusTA effects for arm and shoulder muscles in pyramidotomized or LVST lesioned monkeys to determine whether activation of these structures contributes to the pattern of PStEs reported here.

Comparison with studies of the motor output of the cat reticular formation

As mentioned in the INTRODUCTION, Sprague and Chambers (1954) and Drew and Rossignol (1990a,b) reported that the most common effects of reticular formation stimulation were ipsilateral elbow flexion, contralateral elbow extension, and turning of the head to the stimulated side. In the monkey, the prevalence of flexor PStF with extensor PStS in the proximal arm and shoulder would be consistent with a behavioral response of flexion of the ipsilateral forelimb. Indeed, when PStEs were observed simultaneously in iBic and iTri, the predominant pattern was iBic PStF with iTri PStS. It is important to note, however, that iBic

was the least affected muscle, whereas iTri was among the most commonly affected muscles in the present results. It is uncertain whether the low effectiveness for iBic reflects the actual output of the reticulospinal tract, or merely reflects the low amplitude and short duration of biceps activity involved in the behavioral task, which could have decreased the likelihood of observing PStEs in this muscle. EMG responses were not recorded for the contralateral arm in this study, so it was not possible to measure contralateral responses. On several occasions, however, contractions in the contralateral triceps were visible with repetitive microstimulation. Recordings from the contralateral arm could reveal if extensor facilitation is prevalent contralaterally.

Head movement toward the ipsilateral limb was also noted in response to reticular formation stimulation in the cat (Drew and Rossignol 1990a). In the rhesus monkey, Cowie and Robinson (1994) reported that ipsiversive head rotation was elicited by repetitive microstimulation in and around the region of the NRGc. In the present study, the head was restrained and it was impossible to observe head movement. The most common effects in the upper trapezius muscle, however, would have been consistent with turning of the head to the same side. Contraction of sternocleidomastoid was also observed with stimulus trains at some sites, so it seems likely that head movement would have resulted in these situations if the head had not been restrained.

A difference between the study by Drew and Rossignol (1990a) and the present study is that the cats were at rest when stimulation was applied. Stimulus trains applied at rest are sufficient to allow observation of movement or EMG facilitation, but without activation of the muscle, suppression may be difficult to observe. In fact, Drew and Rossignol rarely observed suppression, and the only cases of suppression noted were in the ipsilateral triceps, a muscle that also demonstrated a prevalence of PStS in the monkey. In the present study, most stimuli were applied during periods of activity. Presumably, higher baseline levels of EMG were present for subjects in the present study, so suppressive and facilitative effects of the EMG may both have been more readily revealed.

In the thalamic cat, responses observed in flexor and extensor muscles during locomotion depended on the phase of locomotion when mPMRF stimulation was applied (Drew and Rossignol 1984). Generally, responses for a muscle were most common when that muscle was most active (e.g., stance for extensors). In the intact, behaving cat, stimulus trains applied to the mPMRF during locomotion typically facilitated contralateral and ipsilateral limb flexors and inhibited ipsilateral limb extensors (Drew 1991). As in the thalamic cat, stimulation was most effective for a muscle when applied in the phase of locomotion in which the muscle was most active. In the present study, no differences in PStEs were observed for different directions of reaching. During locomotion, spinal networks are governed by a central pattern generator, and motor responses to peripheral and supraspinal inputs depend heavily on whether the stimulus is applied during swing versus stance (Forssberg 1979; Gossard et al. 1996; Pearson et al. 1998). Voluntary reaching in different directions within the workspace in front of the animal and against no substantial external load might not involve such strong differences in the state of spinal networks. To determine whether substantially different patterns of output for StimulusTA in the monkey could be observed on the basis of the movement under way, it would probably be necessary for the different reaching movements to be forceful, mimicking the requirements of brachiation; at a minimum, it would probably be necessary for shoulder girdle movements to differ substantially.

Bilateral actions of the reticulospinal tract

Bilateral responses have been consistently reported between forelimb and hindlimb muscles in both decerebrate and intact preparations at rest and during locomotion (Drew 1991; Drew and Rossignol 1984, 1990a,b; Jankowska et al. 2003; Peterson et al. 1975, 1979). The serial and reciprocal responses observed between the ipsilateral and contralateral upper trapezius in

the present study are consistent with previous reports of the bilateral actions of the reticulospinal tract in the cat. Most bilateral responses included contralateral PStF with ipsilateral PStS for both serial and reciprocal responses. Bilateral reciprocal and serial responses are unlike the analogous responses between anatomical antagonists within a limb because bilateral responses could involve commissural interneurons. Jankowska et al. (2003) proposed several pathways, some involving commissural interneurons, through which contralateral responses could be mediated by the reticular formation. Although these observations were made in the lower extremity of the cat, similar pathways could be responsible for bilateral actions in the upper trapezius muscles of the monkey. In one pathway, the reticulospinal tract would simultaneously activate an excitatory commissural interneuron (e.g., to cUTr) and an ipsilateral inhibitory interneuron (e.g., to iUTr), with both interneurons synapsing onto motoneurons. This would cause simultaneous effects bilaterally, resulting in a reciprocal response. The occurrence of serial responses could be explained by monosynaptic excitation of motoneurons on one side in conjunction with oligosynaptic projections to inhibitory interneurons affecting motoneurons on the opposite side. The overall finding in the present results, that PStF began sooner than PStS, is consistent with an inhibitory interneuron being required to mediate PStS.

Whether these complex actions could represent the effects of a single mPMRF neuron is uncertain, given that the present results were produced by stimulation. Single reticulospinal axons can project to both sides of the spinal cord (Matsuyama et al. 1997, 1999), so the anatomical substrate for this is present. Alternatively, bilateral responses could be mediated by several reticulospinal neurons synapsing at the segmental level on separate interneuron and motoneuron populations. The use of spike-triggered averaging (SpikeTA) could help reveal the circuitry of these pathways because this method can examine the motor output of a single neuron, if synchrony effects are excluded (Fetz and Cheney 1980).

Ipsilateral upper trapezius

Compared with the other muscles included in the present study, the ipsilateral upper trapezius (iUTr) demonstrated a unique pattern of PStEs. Although suppression was the most prevalent response for iUTr, the strongest facilitation events observed for all muscles were in iUTr. Single-pulse currents as low as 10 μ A produced strong, short-latency PStF events, and in some cases, a muscle twitch could be visually observed for single pulses with these low stimulus currents. This suggests that, in the primate, ipsilateral upper trapezius motoneurons may receive monosynaptic projections from the mPMRF. This is consistent with results reported by Peterson et al (1979) of monosynaptic excitation of cat neck motoneurons and motoneurons projecting in the spinal accessory nerve. Peterson et al. (1979) reported that neck sites were distributed throughout the mPMRF, but were concentrated in the ipsilateral mPMRF, in a position ventral and caudal to the abducens nucleus.

Comparison with primary motor cortex and red nucleus

Because reticulospinal neurons are caudal to the red nucleus and conduction velocities have been reported to be faster for reticulospinal axons (Shapovalov 1972), PStF onset latencies could be expected to be earlier for the mPMRF than for the red nucleus. In the red nucleus, average onset latencies for the proximal and distal arm combined were reported to be 7.9 ms for PStF and 12.3 ms for PStS (Belhaj-Saif et al. 1998). The average PStF onset latency of 7.1 ms for the mPMRF was similar to that for the red nucleus, although PStS was considerably earlier for the mPMRF (8.4 ms). These figures, however, may not provide an accurate comparison for these 2 regions because different muscles were included in the latency measurements, and latencies for specific muscles should be considered instead. For the shoulder muscles, onset latencies were slightly later for the mPMRF (7.9 ms; iPDlt, iADlt, iLat) than for the red nucleus (7.3 ms). PStF onset latencies of 8.0 ms for iBic and iTri were

almost equal to PStF latencies for the elbow muscles from the red nucleus (8.2 ms). Thus latencies were similar for similar muscles.

The effects of StimulusTA of proximal arm and shoulder muscles from the mPMRF, however, were generally opposite to those reported for the red nucleus. StimulusTA studies in red nucleus of the monkey have consistently reported a clear extensor bias throughout the arm and shoulder (Belhaj-Saif et al. 1998; Cheney 1980; Cheney et al. 1991; Fetz et al. 1989). Belhaj-Saif et al. (1998) observed PStEs in the muscles of the wrist, elbow, and shoulder joints, with PStEs most frequent in distal arm muscles. PStF was most frequent in extensor muscles for the shoulder, elbow, and wrist, with the highest percentages of PStF shown distally. Conversely, PStF was uncommon in flexors, which showed higher proportions of PStS. Overall, PStS effects were less frequent than PStF effects. The authors concluded that the red nucleus preferentially controls extensor muscles in the distal and proximal arm, with a preference for distal arm muscles.

StimulusTA of proximal arm and shoulder muscles has also been performed from the primary motor cortex of the monkey (Park et al. 2001). Because this was a mapping study, only PStF events were analyzed and patterns of PStEs were not analyzed among muscles and onset latencies were not reported. Using SpikeTA in the primary motor cortex, McKiernan et al. (1998) demonstrated that postspike effects can be observed in proximal arm and shoulder muscles, although less frequently than in the distal arm. Interestingly, the reported pattern of postspike effects was similar to the pattern of poststimulus effects observed from the mPMRF. This included a prevalence of flexor facilitation and extensor suppression in the muscles of the proximal arm and shoulder. McKiernan et al. reported that, of the neurons that produced postspike effects in proximal muscles, the majority also produced postspike effects in wrist and hand muscles. One explanation for this similarity could be that the PStEs reported in the present study represent the effects of CST collateral stimulation. As discussed above, however, evidence suggests that the effects of mPMRF stimulation are not a result of CST collateral stimulation. The tendency for postspike effects to be observed simultaneously in proximal and distal muscles suggests that CST collateral stimulation would activate both proximal and distal limb muscles. The similarity in these results may indicate that, for proximal control, the primary motor cortex and the mPMRF could work synergistically to produce similar motor output patterns, with the primary cortex directing the reticulospinal system through CST collaterals and corticoreticular projections.

Clinical relevance

In humans, there are no direct data on the consequences of electrical stimulation in the mPMRF, but inferences may be drawn from the motor patterns present in the paretic limb of patients with hemiplegia after stroke. Dewald et al. (1995) demonstrated that stroke patients display a predominance of certain muscle synergies after stroke and argued that increased reliance on the reticulospinal systems for voluntary control might explain this dominance. When the subjects studied by Dewald et al. (1995) elevated their shoulder, they typically flexed their elbow, and had great difficulty recruiting the elbow extensors along with the shoulder elevators. This is consistent with the finding in the present study of a prevalence of simultaneous iBic PStF and iTri PStS from the same stimulation site and the strong PStF effects seen in iUTr, but not with the prevalence of PStS in iUTr.

As demonstrated in these results and other studies (Matsuyama et al. 1997; Wilson and Peterson 1981), outputs from the mPMRF can have bilateral effects. This bilateral control could be an important substrate for recovery of function after stroke (Dewald et al. 1995; Freund and Hummelsheim 1985) because either side of the cortex could presumably access both sides of the body through reticulospinal outputs. Thus the present data could support the hypothesis that the motor patterns common in the upper extremity after stroke might represent increased

reliance on outputs from the mPMRF for voluntary control. Further study is required to understand how reticulospinal outputs contribute to the control of reaching in the normal nervous system as well as after stroke.

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FIG. 1. Representative sample of EMG during task performance. EMG recorded from Monkey C is represented for a 5-s segment of the task. Although this record did not include stimulation, a trace-labeled stimulation is provided to illustrate the frequency of stimulation in the context of the task. iUTr, ipsilateral upper trapezius; cUTr, contralateral upper trapezius; iLat, ipsilateral latissimus dorsi; iMTr, ipsilateral middle trapezius; iPDlt, ipsilateral posterior deltoid; iTri, ipsilateral triceps; iBic, ipsilateral biceps.

FIG. 2.

Anatomical location of effective stimulation sites for iUTr (subject D). Key indicates the type of response represented by each symbol. In *A*, stimulation sites for one plane (AP, -1) are superimposed on a corresponding brain stem section. In *B* and *C*, all stimulation sites are illustrated for the anterior–posterior (AP, *B*) and medial–lateral (ML, *C*) planes. Arrow in *B* (labeled *A*) indicates the plane illustrated in *A*. Approximate location of the facial nucleus (VII), abducens nucleus (VI), inferior olive (IO), and the pyramidal tract (Pyr) are indicated in *B* and *C*. AP, ML, and dorsal–ventral (DV) scales are in Horsley–Clarke stereotaxic coordinates. IV, fourth ventricle; Pp, nucleus prepositus; MVe, LVe, SVe, and IVe, medial, lateral, superior, and inferior vestibular nuclei, respectively; Sp5, spinal trigeminal nucleus.

FIG. 3.

Detection of poststimulus events. For each trace, the mean EMG level for the baseline period is illustrated by a solid horizontal line, and dotted horizontal lines above and below the mean indicate ± 2 SD. Filled bars represent periods of PStF; open bars represent PStS. Stimuli were applied at $20 \mu\text{A}$. iUTr, ipsilateral middle trapezius; iADlt, ipsilateral anterior deltoid. SDPk for events: iUTr (17.6), cUTr (27.4).

FIG. 4.

A: number of responses by onset latency for all acceptable events detected in response to actual stimulation (StimulusTA, filled bars) and to randomly timed fake stimuli from the same data files (RandomTA, open bars). Dashed horizontal line is drawn at a level 2 SDs above the mean number of RandomTA events per 2-ms bin. *B*: distribution of response amplitudes for StimulusTA and RandomTA events with onsets between 3.5 and 12.5 ms. Amplitude is expressed in terms of the variable mean percentage change (MPC) (see METHODS); the mean amplitude expressed as a percentage change from the baseline.

FIG. 5.

Histograms of PSTEs by onset latency for each muscle; bin size is 2 ms, and there are 5 responses per vertical tick mark. Only events with onsets before 25 ms are represented. PSTf is represented by upward, filled bars; PSTs is represented by downward, empty bars. For each muscle, the number of sites stimulated for which a recording of that muscle's EMG was available is noted as the number of sites tested. Percentage of those sites for which a response occurred with an onset between 3.5 and 12.5 ms is indicated as the percent effective.

FIG. 6.

Proportions of PStF (solid line) and PStS (dashed line) events by muscle. Only events with onset latencies from 3.5 to 12.5 ms are represented. For the type of response that was most prevalent for each muscle, the data point is marked with a symbol (● for PStF, Δ for PStS), and the number of times that response was observed is indicated as a fraction of the total number of responses observed for that muscle.

FIG. 7.

Typical stimulus-triggered average. Filled bars represent PStF; open bars represent PStS. Stimuli were applied at 25 μ A. SDPk of events: iBic (4.8), iTri (10.6), iLat (5.6), iUTr (7.8), cUTr (25.4).

FIG. 8. Additional examples of stimulus-triggered averages. Filled bars represent facilitation and open bars suppression. *A*: stimuli were applied at $30 \mu\text{A}$. SDPk of events: iTri (5.8), iPDlt (4.6), iLat (8.2), iUTr (5.8). *B*: stimuli were applied at $30 \mu\text{A}$. SDPk of events: iBic (11.5), iADlt (6.5), iMTr (8.6), cUTr (11.5).

FIG. 9.

Large-amplitude, short-latency response in ipsilateral upper trapezius. Stimuli were applied at $30 \mu\text{A}$. SDPk of events: iUTr (85.0), iMTr (4.4).

FIG. 10. Bilateral responses in upper trapezius. *A*: reciprocal response of iUTr PStS and cUTr PStF. Stimuli were applied at 40 μ A. SDpk of events: iUTr (8.4), cUTr (8.4) *B*: serial response of iUTr PStS and cUTr PStF. Stimuli were applied at 30 μ A. SDpk of events: iUTr (15.7), cUTr (18.9).

TABLE 1

Onset latency and duration (ms) of poststimulus events

Muscle		<i>n</i>	Facilitation	<i>n</i>	Suppression
iBic	Onset	8	7.49 ± 2.06	0	—
	Duration		8.88 ± 10.28		—
iADlt	Onset	10	7.87 ± 2.84	3	7.07 ± 2.58
	Duration		6.63 ± 3.63		3.89 ± 1.35
iPDlt	Onset	7	6.75 ± 1.48	10	7.52 ± 1.68
	Duration		4.57 ± 1.57		4.60 ± 2.30
iTri	Onset	1	5.06 ± —	21	7.48 ± 1.64
	Duration		10.58 ± —		6.72 ± 3.27
iLat	Onset	3	10.10 ± 2.49	13	8.84 ± 1.10
	Duration		7.34 ± 5.56		8.96 ± 7.65
iUTr	Onset	13	7.28 ± 2.55	36	9.51 ± 2.02
	Duration		14.39 ± 9.20		7.79 ± 4.36
cUTr	Onset	38	6.72 ± 1.92	8	8.04 ± 2.90
	Duration		5.16 ± 3.17		5.49 ± 3.02
iMTr	Onset	14	5.91 ± 2.05	8	9.11 ± 1.32
	Duration		5.80 ± 3.89		5.56 ± 2.78
cMTr	Onset	2	8.30 ± 0.00	4	9.21 ± 2.21
	Duration		2.70 ± 0.16		8.26 ± 4.54

Values are means ± SD.