Effective intracortical microstimulation parameters applied to primary motor cortex for evoking forelimb movements to stable spatial end points

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Van Acker GM 3rd, Amundsen SL, Messamore WG, Zhang HY, Luchies CW, Kovac A, Cheney PD. Effective intracortical microstimulation parameters applied to primary motor cortex for evoking forelimb movements to stable spatial end points. J Neurophysiol 110: 1180–1189, 2013. First published June 5, 2013; doi:10.1152/jn.00172.2012.— High-frequency, long-duration intracortical microstimulation (HFLD-ICMS) applied to motor cortex is recognized as a useful and informative method for corticomotor mapping by evoking natural-appearing movements of the limb to consistent stable end-point positions. An important feature of these movements is that stimulation of a specific site in motor cortex evokes movement to the same spatial end point regardless of the starting position of the limb. The goal of this study was to delineate effective stimulus parameters for evoking forelimb movements to stable spatial end points from HFLD-ICMS applied to primary motor cortex (M1) in awake monkeys. We investigated stimulation of M1 as combinations of frequency (30–400 Hz), amplitude (30–200 μA), and duration (0.5–2 s) while concurrently recording electromyographic (EMG) activity from 24 forelimb muscles and movement kinematics with a motion capture system. Our results suggest a range of parameters (80–140 Hz, 80–140 μA, and 1,000-ms train duration) that are effective and safe for evoking forelimb translocation with subsequent stabilization at a spatial end point. The mean time for stimulation to elicit successful movement of the forelimb to a stable spatial end point was 475.8 ± 170.9 ms. Median successful frequency and amplitude were 110 Hz and 110 μA, respectively. Attenuated parameters resulted in inconsistent, truncated, or undetectable movements, while intensified parameters yielded no change to movement end points and increased potential for large-scale physiological spread and adverse focal motor effects. Establishing cortical stimulation parameters yielding consistent forelimb movements to stable spatial end points forms the basis for a systematic and comprehensive mapping of M1 in terms of evoked movements and associated muscle synergies. Additionally, the results increase our understanding of how the central nervous system may encode movement.

motor control; primary motor cortex; primate; stimulation; EMG; forelimb

corticomotor connectivity between neurons in primary motor cortex (M1) and muscles has been mapped previously with various forms of electrophysiological methods, tracer studies, and histological approaches (Cheney and Fetz 1985; Donoghue et al. 1992; Penfield and Boldrey 1937; Rathelot and Strick 2006; Woolsey et al. 1952). While early clinical electrophysiological approaches utilized surface stimulation of the cortex to evoke grossly observable responses (Penfield and Boldrey 1937; Woolsey et al. 1952), the introduction of intracortical microstimulation (ICMS) has permitted more refined mapping of cortical output to muscles (Asanuma and Sakata 1967). Short trains of high-frequency ICMS, often 10 cathodal pulses at 330 Hz, have been used to evoke twitchlike responses for cortical mapping and other purposes (Asanuma et al. 1976; Strick and Preston 1978). Such parameters have been used frequently, as consistent parameters have allowed for comparison of results between laboratories and studies. More recently this method of ICMS has been modified by applying ICMS trains with longer durations (500 ms) that more closely match the timescale of voluntary movements (Ethier et al. 2006; Graziano et al. 2002, 2005). These high-frequency, long-duration (HFLD)-ICMS trains produce movements of the limbs characterized by having a common spatial end point for a particular cortical site regardless of the starting position of the limb.

In the present study, our aim was to identify effective parameters for HFLD-ICMS applied to the monkey forelimb representation in M1 that yield translocation and subsequent stabilization of the forelimb at discrete spatial end points. We applied stimulation as combinations of frequency (30–400 Hz), amplitude (30–200 μA), and duration (0.5–2 s) while concurrently recording the electromyographic (EMG) output to 24 forelimb muscles as well as the stimulus-evoked limb kinematics with a Vicon motion capture system. Our results suggest a range of stimulus parameters for M1 forelimb representation that are both safe and effective for evoking movement and subsequent stabilization of the forelimb at a spatial end point in an awake monkey. These parameters are 80–140 Hz, 80–140 μA, and 1,000 ms. The median successful frequency and stimulus intensity for all successful trials were 110 Hz and 110 μA, respectively, and the mean time for stimulation to elicit successful movement of the forelimb to a stable spatial end point was 475.8 ± 170.9 ms. Attenuated parameters resulted in inconsistent, truncated, or undetectable movements, while intensified parameters yielded no additional movement end-point data and increased the potential for large-scale physiological spread and adverse focal motor effects. Establishing stimulation parameters that yield consistent forelimb movements to stable spatial end points formed the basis for a systematic and complete mapping of forelimb movement rep-
EXPERIMENTAL PROCEDURES

Behavioral task. Data were collected from two male rhesus macaques (Macaca mulatta; ~9 kg each, ages 12 and 4 yr) performing a reach and prehension task that required coactivation of proximal and distal forelimb muscles while also yielding discrete spatial locations to cue stimulus trains. Training procedures and the behavioral task have been described in detail previously (Belhaj-Saïf et al. 1998; McKiernan et al. 1998). Briefly, the monkey was seated in a custom primate chair within a sound-attenuating chamber with his left arm comfortably restrained while his right arm retained freedom of movement. To discourage the monkey from interfering with reflective motion capture spheres attached to his arm, a custom face mask barrier was installed on the chair that contained a small hole through which the monkey could feed himself. To receive a food reward, the monkey initiated the task with his right hand by depressing a homeplate lever located at waist height directly in front of him for 1-s duration, triggering the release of a food pellet into a food well located at shoulder height requiring full extension of the arm. After retrieval and consumption of the food reward, the monkey returned his hand to the homeplate for subsequent trials. Performance was guided by audio and visual cues.

Surgical procedures. After training, an MRI-compatible titanium steel chamber allowing 30-mm diameter of dura exposure, and exploration of the underlying cortical area, was implanted stereotaxically over the M1 of the left hemisphere of each monkey with procedures described in detail previously (Park et al. 2001). Briefly, the chamber was anchored to the skull with titanium screws and dental acrylic and was centered over the hand area of M1 in the left hemisphere. In addition, threaded titanium nuts were attached over the occipital aspect of the skull with titanium screws and dental acrylic. These nuts provided a point of attachment for a flexible head restraint system during data collection (McKiernan et al. 1998, 2000). The chambers were centered at anterior 17.7 mm, lateral 27.2 mm, and 26° to the sagittal plane for monkey X and anterior 16 mm, lateral 22 mm, and 30° to the sagittal plane for monkey A.

Twenty-four muscles of the right shoulder and forelimb were each implanted with two multistranded stainless steel wires (Cooner Wire, AS632). Both monkeys were implanted under sterile conditions with a cranial subcutaneous implant technique described previously (Park et al. 2000). Briefly, all wires were stripped of ~2–3 mm of insulation and tunneled subcutaneously from a cortical connector (Amphenol, Wallingford, CT) to each muscle, where the wires were inserted into the muscles a distance of ~2–3 cm, with ~5-mm separation of the two wires in each muscle. The cortical connector module was secured with dental acrylic near the cortical recording chamber. We tested the placement accuracy of each electrode pair by observing appropriate muscle twitches that resulted from application of short stimulus trains (Grass SD9 Stimulator). EMG activity was recorded from five shoulder muscles: pectoralis major (PEC), anterior deltoïd (ADE), posterior deltoïd (PDE), teres major (TMJ), and latissimus dorsi (LAT); seven elbow muscles: biceps short head (BIS), biceps long head (BIL), brachialis (BRA), brachioradialis (BR), triceps long head (TLO), triceps lateral head (TLAT), and dorsopalmaris clearans (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 (ED23), extensor digitorum 4 and 5 (ED45), 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. Prior to each implant surgery, the monkey was administered ketamine (10 mg/kg im), atropine (0.04 mg/kg im), and medetomidine (0.05 mg/kg im) for transportation purposes and subsequently isoflurane gas for the duration of the surgery. Each monkey received prophylactic antibiotic (penicillin, 6,000 U/kg sc) 10 h before surgery, 1 h directly after surgery, and 3 days after surgery. Postoperatively, the monkeys were given analgesics (0.01 mg/kg buprenorphine im and 5 mg/kg carprofen sc). All surgeries were performed in a facility accredited by the Association for Assessment and Accreditation of Laboratory Animal Care with full sterile procedures. All procedures were reviewed and approved by the University of Kansas Medical Center Institutional Animal Care and Use Committee.

Recording forelimb kinematics. Limb kinematics were monitored and recorded with a Vicon (Oxford, UK) motion capture system. For the purposes of this study, a virtual sphere located on the dorsal tubercle of the radius was calculated and used to evaluate limb kinematics as well as the spatial end point resulting from HFLD-ICMS applied to each cortical site. The three-dimensional coordinates of this virtual sphere were calculated with point cluster technique as described previously (Andriacchi et al. 1998; Senesh and Wolf 2009). Briefly, a cluster of reflective spheres were attached to the forearm of each monkey. The three-dimensional coordinates of the spheres in the cluster, collected at a sampling rate of 100 Hz with four Vicon MX+ cameras with reconstruction done off-line with Vicon Nexus software, were used to triangulate the coordinates of the virtual sphere located on the dorsal tubercle of the radius, which was identified during static trials at the start of each recording session. The dorsal tubercle of the radius was used as a surrogate for end-point position of the hand in space. Utilizing subsets of the numerous wrist markers to calculate the spatial position of the reference point (dorsal tubercle of the radius) reduced the need for the dorsal tubercle of the radius to be within view of any particular set of Vicon cameras in order to be monitored.

HFLD-ICMS protocol. One thousand six hundred and twenty HFLD-ICMS trains were applied to 19 distinct cortical sites within the right forelimb representation of M1 in the left hemisphere (Fig. 1) of two rhesus macaques performing a reach and prehension task over the course of the study. Stimulation was applied through glass-insulated platinum-iridium electrodes suitable for single-unit recording (FHC, Bowdoin, ME), with typical impedances of 0.7–1.5 MΩ at the start of each recording session. We positioned the electrodes with an X–Y positioner secured to the chamber for the duration of each recording session and advanced the electrode into the brain with a manual hydraulic microdrive (FHC) until the electrode tip was located in cortical lamina V, or ~1.5 mm below the surface of the brain. Location of layer V was determined by depth, audio cues (Grass AM8 Audio Monitor), visual cues (oscilloscope display of large spike waveforms), and finally poststimulus effects in stimulus-triggered averages (STAs) of EMG activity computed at an intensity of 15 μA and a stimulus frequency of 10 Hz (Park et al. 2001). HFLD-ICMS was applied when the monkey’s hand was at one of three task positions (homeplate, food well, or mouth), and the location that was furthest from the stimulus-evoked spatial end point was chosen once a test stimulation trial elicited a detectable movement. Because the position at the food well was on the periphery of the monkey’s workspace, this location was used most frequently for stimulation onset.

At each cortical site we applied systematic combinations of frequency (30–400 Hz), amplitude (30–200 μA), and duration (0.5–2 s) in order to delineate parameters that yielded forelimb movement with subsequent stabilization. Individual stimuli for each stimulus train were symmetrical cathodal biphasic pulses: initial negative pulse 0.2 ms in duration followed by a positive pulse 0.2 ms in duration. Stimulus train duration of 1 s was revealed early in the study to be an optimal epoch for assessing the adequacy of the stimulus intensity and frequency parameters. A 500-ms stimulus train duration often resulted in
in movements that were truncated relative to spatial end points achieved with longer durations and was therefore too short to reliably determine a spatial end point for many elicited movements. Movements to spatial end points were always achieved with stimulus durations of 1,000 ms, and therefore longer durations were unnecessary and increased the risk of adverse focal motor effects. Finally, once the forelimb reached the spatial end point, the time remaining in the 1,000-ms train was used to ensure that the forelimb was locked in the final posture for the duration of stimulation and that stimulation was not evoking a truncated movement or a movement to an unstable end point.

While we initially explored frequencies ranging from 200 to 400 Hz as well as intensities ranging from 150 to 200 μA, we concluded that these parameter ranges were unnecessarily high for achieving a stable stimulus-evoked end point and that these parameters also increased the potential for adverse focal motor effects. Therefore each parameter set collected for data analysis in this study was a combination within a frequency range of 50–170 Hz, a stimulus intensity range of 15–200 μA, and a train duration of 1,000 ms.
range of 30–150 μA, and a 1-s duration. Five trials were conducted for each HFLD-ICMS parameter set. Occasionally, an additional set of five stimulation trials were repeated at the same cortical site later in the study session to allow comparison of movement end points between the beginning and end of the stimulation recording session.

**Determining successful stimulus parameters for evoked movements.** The kinematics of HFLD-ICMS-evoked wrist movement (marker on the dorsal tubercle of the radius) were used to assess successful spatial end points achieved through stimulation of M1. HFLD-ICMS-evoked movement trials were deemed successful if the stimulus parameters applied to the M1 site were sufficient to translocate the monkey’s forelimb to a spatial location distinct from its location at the initiation of stimulation and sufficient to maintain the limb at the stimulus-evoked location for the duration of stimulation. Attenuated parameters resulted in incomplete, truncated, or undetectable movements of the forelimb, often resulting in the monkey overcoming the stimulated movement and returning to the voluntary movement task. Intensifying parameters beyond those deemed successful at each cortical site also yielded similar end points. However, intensified parameters increased the potential for adverse focal motor effects, possibly due to extensive physiological spread along horizontal cortical collaterals exacerbated by excessive stimulus frequency. Therefore, our goal was to delineate the safe and effective range of parameters that yielded movement and subsequent stabilization of the forelimb for the duration of stimulation.

The specific success criteria we used required, first, that stimulus-evoked movement velocity reach a level of ≥40% of the average maximum stimulus-induced velocity within the first 500 ms of stimulation onset to indicate adequate stimulus-induced movement. The average maximum stimulus-induced velocity was calculated from a subset of ~25% of the data for which we determined success based on individual trial velocity data. An iterative classification process was used because we needed first to determine qualitatively the parameters that resulted in a stable posture and subsequently to create an algorithm that matched closely our visual interpretation. This was important particularly due to the fact that there were multiple points within the evoked movement velocity profile for which the algorithm required modeling to fit movements to stable end points. Therefore, we first determined qualitatively which evoked movements were stable, then generated an algorithm that distinguished these movements as stable, and finally retested to ensure that the algorithm was accurately grouping the movements as successful or unsuccessful as determined qualitatively. This iterative process allowed for final analysis of all trials using one algorithm with consistent velocity thresholds.

The second criterion was that, on the slowing phase of movement, the velocity had to cross below a threshold of 372.1 mm/s, or 25% of the average maximum stimulus-induced velocity of 1,488.1 mm/s based on data from both monkeys. Finally, once this lower threshold was crossed, the velocity of the movement had to remain below this 25% threshold for the remainder of the applied stimulus train to ensure that a stable spatial end point had been achieved (Fig. 2). A 25% threshold was used to allow for oscillations of the wrist about a single end point, which occurred often once the limb reached the spatial end point. This threshold was low enough to separate the oscillations from voluntary movements superimposed on stimulus-driven movements within the epoch of stimulation. Time to spatial end-point stabilization for successful trials was measured at the point where the velocity of the stimulus-evoked movement crossed the threshold of 25% toward achieving a stable end-point position. These criteria provided an objective and reproducible method of identifying successful trials that closely matched our subjective visual assessment.

**Stimulus-triggered averages.** StTAs of EMG activity (Park et al. 2001) were acquired for all implanted muscles from stimuli applied throughout all phases of the reach and prehension task. StTAs were used to help confirm positioning of the electrode in lamina V and to determine cortico-muscle connectivity of corticospinal cells directly surrounding the electrode tip. StTAs were obtained at 10 Hz and at current intensities that matched those used for each HFLD-ICMS train applied at the same site. In addition, muscle facilitation maps (Fig. 1, A and B) were based on StTAs collected at 15 and 30 μA with stimulus sites at 1-mm intervals on the surface of the precentral gyrus and 0.5-mm vertical intervals down the bank of the central sulcus. EMG activity was filtered from 30 Hz to 1 kHz, digitized at 4 kHz, and full-wave rectified. Individual stimuli for the StTAs were symmetrical biphasic pulses: initial negative pulse 0.2 ms in duration followed directly by a positive pulse 0.2 ms in duration. StTAs were based on a minimum of 1,000 trigger events. Averages were compiled using a 60-ms epoch of which 20 ms prior to the trigger was considered baseline. StTAs were identified as having a significant poststimulus effect (PStE) if the peak or trough of the effect exceeded ±5 SD of the baseline for a period of ≥0.75 ms as described previously for moderate to large effects (Park et al. 2004).

**Measurement of EMG cross talk.** We evaluated cross talk between EMG electrodes by constructing EMG-triggered averages. This pro-

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**Fig. 2.** Example of velocity profiles of the monkey’s wrist (dorsal tubercle of the radius) in space during 3 separate trials using different parameters applied to the same cortical site. Stimulation is represented by vertical lines under “HFLD-ICMS,” and stimulus duration is represented by gray background underlying velocity tracings. A successful trial is defined as stimulation resulting in translocation of the limb to a spatial end point with subsequent stabilization for the duration of the stimulation (see EXPERIMENTAL PROCEDURES). The average maximum velocity was 1.49 m/s, while the 25% and 40% thresholds were 0.37 and 0.60 m/s, respectively. The velocity profile shown by the solid line represents a successful trial, whereas those shown by the dashed lines represent unsuccessful trials. HFLD-ICMS, high-frequency, long-duration intracortical microstimulation.
The procedure used the motor unit potentials from one muscle as triggers for compiling averages of rectified EMG activity of all other muscles. Criteria established previously (Buys et al. 1986) were used to eliminate effects that might have been affected by cross talk. To be accepted as a valid PSIE, the ratio of poststimulus facilitation (PSF) between the test and trigger muscles must have exceeded the ratio of their cross talk peaks by a factor of 2 or more. On the basis of this criterion, FDI in monkey X was removed from the analysis.

RESULTS

Success rate for parameter pairings. The ratio of successful HFLD-ICMS-evoked movement trials to total trials was calculated for each frequency and current intensity parameter pairing. A successful trial was defined as one in which HFLD-ICMS produced translocation of the arm to a new end-point position that remained stable for the duration of stimulation (see EXPERIMENTAL PROCEDURES). Figure 3 illustrates the success rate for each parameter pairing color coded as a ratio of successful trials to total trials for each pairing. Total trials attempted are noted in the center of each parameter pairing box. The results reveal a clear boundary of the lower range of stimulus parameters that yield successful forelimb movements to stable spatial end points from HFLD-ICMS applied to M1 cortex. At a given site, once the threshold of successful stimulus parameter pairings was found, increasing stimulus parameters at that site resulted in the same spatial end-point, although increasing the risk for adverse focal motor effects. Because of this risk, a clear upper boundary was not aggressively sought. Successful stimulus parameters primarily fell within the frequency range of 80–140 Hz coupled with a stimulus intensity range of 80–140 mA. For successful HFLD-ICMS-evoked movements of the forelimb, the mean time from stimulus onset to the arm reaching a spatial end-point position was 475.8 ± 170.9 ms, and the range was 110–940 ms. The mean successful frequency, calculated with a weighted average based upon the ratio of successful to total trials for each parameter pairing, was 117.6 ± 23.2 Hz, and the mean successful stimulus intensity was 108.3 ± 24.4 mA. Additionally, the median successful frequency and stimulus intensity for all trials were 110 Hz and 110 mA, respectively. Attenuated parameters resulted in inconsistent, truncated, or undetectable movements of the forelimb, often resulting in the monkey overcoming the stimulated movement and returning to the volitional movement task. Intensified parameters beyond the optimal range identified above yielded no additional benefit while increasing the potential for physiological spread and adverse focal motor effects, and therefore were avoided.

Success rate for parameter pairings for an individual site. Figure 4 illustrates stimulus parameter pairings that led to successful spatial end points at an individual cortical site. In this example, 158 stimulation trials were applied to cortical site 6 of monkey X (Fig. 1B). The range of stimulus parameters that evoked successful spatial end points were relatively consistent across M1 cortical sites. For each cortical site at which stimulation was applied in this study, a locus of successful stimulus parameter pairings was evident. The ranges of parameters that yielded the highest success rate for the cortical site illustrated in Fig. 4 were 80–140 Hz and 100–140 mA, with a mean time to spatial end-point stabilization of 556.9 ± 49.9 ms. The mean successful frequency and amplitude at this site were 127.5 ± 18.5 Hz and 109.7 ± 25.9 mA, respectively, and the median successful frequency and amplitude were 120 Hz and 120 mA, respectively.

Effect of stimulus parameters on peak movement velocity. To characterize the relationship between stimulus parameters and movement velocity of the forelimb during stimulation, we first applied a multiple regression analysis to all successful parameter pairings at all sites for both monkeys. Figure 5 illustrates a density plot of stimulus parameter pairings color coded as the

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**Fig. 3.** Success rate for HFLD-ICMS pairings for both monkeys: density plot of stimulus parameter pairings color-coded as a ratio of successful trials to total trials for each pairing. Stimulus train duration was 1 s for each parameter pairing. Total trials for each parameter pairing are listed in the center of each square. On the ratio scale, 1.0 is equal to a success rate of 100% for that stimulus parameter combination. NT, parameters not tested.

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peak stimulus-induced velocity for each parameter pairing for both monkeys averaged over the number of trials listed in the center of each square. A stimulation duration of 1 s was applied for each parameter pairing, and only trials that yielded successful spatial end points were included. Combining all data, Pearson linear correlation analysis assessing peak velocity relative to stimulus frequency \((r = 0.1054, P = 0.4070)\) or to stimulus intensity \((r = 0.1906, P = 0.1313)\) did not yield statistically significant relationships, although there is a clear tendency evident from Fig. 5 for velocity to increase in going from the lower left corner of the plot to the upper right corner. However, as illustrated in Fig. 6, data collected from the single cortical site 5 of monkey X (Fig. 1B), for which multiple regression was used to calculate the effect of the combination of stimulus frequency and intensity on velocity, yielded a significant correlation between stimulation parameters and velocity \((R^2 = 0.8187, P < 0.0001)\). This suggested that significant variance between stimulus parameters and velocity may have been obscured or washed out by combining data from all cortical sites and both monkeys.

**Fig. 4.** Success rate for HFLD-ICMS parameter pairings at 1 cortical site (site 6 in monkey X, Fig. 1): density plot of stimulus parameter pairings color-coded as a ratio of successful trials to total trials for each pairing. Stimulus train duration was 1 s for each parameter pairing. Total trials for each parameter pairing are listed in the center of each square. On the ratio scale, 1.0 is equal to a success rate of 100% for that stimulus parameter combination.

**Fig. 5.** Peak velocity for successful HFLD-ICMS parameter pairings for both monkeys: density plot of stimulus parameter pairings color-coded as the maximum velocity for each pairing averaged over the number of trials listed in the center of each square. Only successful trials were included. Stimulus train duration was 1 s for each parameter pairing.
To further investigate whether the monkey or cortical site affected variations in velocity, we used an ANOVA to look at the effect of frequency, stimulus intensity, and cortical site on the stimulus-evoked movement velocity. A four-way ANOVA showed significant effects ($P < 0.05$) for each independent variable of frequency, stimulus intensity, and cortical site. We further investigated this, using a Tukey’s multiple-group comparison with a Bonferroni correction, in which case we found that the significant differences observed did not come from monkeys specifically; rather, they arose from the cortical sites. These data are consistent with prior long-duration microstimulation studies involving oculomotor and forelimb movements, revealing that higher stimulus frequency and intensity at a given site results in increased movement velocity.

**HFLD-ICMS effect on circuitry not affected directly by stimulation.** Successful spatial end points as calculated in this study were unattainable at a number of sites in M1. HFLD-ICMS applied to M1 cortical sites that yielded either solely proximal or solely distal muscle facilitation, as determined with StTA mapping, were more likely than proximal-distal cofacilitation (PDC) sites (Fig. 1) to yield stimulus-evoked movements with superimposed voluntary activity. For example, if we applied stimulation to an area assessed by StTA to yield distal forelimb facilitation, the likelihood of achieving a spatial end point of the wrist marker was reduced compared with sites in or close to PDC sites. This appeared to be due to the monkey’s ability to retain voluntary control of the joint associated with the muscles that were not affected directly by stimulation. At such purely distal representation sites, the monkey often preserved the ability to move his shoulder and/or elbow, while his distal muscles were fully stimulus activated and apparently locked in the stimulus-evoked posture. As a consequence, the monkey was able to move the virtual sphere located on the wrist continuously during stimulation by moving his shoulder and/or elbow joints. The result was an unsuccessful trial. Ability to move the proximal muscles under voluntary control while the distal muscles appeared to be locked into a stimulus-driven posture was observed at 15 of 45 (33.3%) and 10 of 31 (32.3%) distal-only cortical sites (determined via StTA mapping) for monkeys A and X, respectively, using parameters that normally would produce a successful trial. Conversely, stimulation at 15 of 35 (42.9%) and 15 of 37 (40.5%) proximal-only cortical sites for monkeys A and X, respectively, resulted in a locked posture of proximal muscles while leaving distal muscles accessible to voluntary control. These results include data from all cortical sites explored throughout the entire mapped M1 in both monkeys. However, not every proximal- or distal-only site based on StTA effects responded in this manner, as some yielded both proximal and distal muscle activation when HFLD-ICMS was applied. Broadened activation of muscles with repetitive stimulation is likely due to physiological spread through neural networks that connect proximal and distal muscles for coordinated multijoint limb movements.

**DISCUSSION**

The goal of this study was to determine effective HFLD-ICMS parameters applied to M1 that yield translocation and subsequent stabilization of the forelimb at a fixed end point within the monkey’s workspace. The use of HFLD-ICMS to study motor output has gained traction as an additional technique to include with other electrical stimulation methods such as TMS, high-frequency, short-duration ICMS (HFSD-ICMS), and StTA in studying cortical encoding of movement (Ether et al. 2006; Graziano et al. 2002, 2005; Tehovnik and Lee 1993; Thier and Andersen 1998). Delineating stimulation parameters that translocate the limb and subsequently stabilize it at a spatial end point provides a foundation for selection of appropriate parameters for systematic mapping of M1 output in terms of HFLD-ICMS-induced movements. We would like to
point out that, because of the large number of stimulation combinations applied to each cortical site in this study, a limited number of cortical sites were investigated. While the findings were relatively consistent across sites, and the successful parameters were used effectively in a subsequent study for the systematic mapping of M1, appropriate caution should be maintained when interpreting the results of this study.

Mechanism of stimulus-evoked movement. In this study we determined the effective HFLD-ICMS parameters that, when applied to M1 cortex, would supplant volitional movement of the forelimb with movement induced by stimulation. This replacement of volitional movement with stimulated movement requires elimination or interruption of the subject’s voluntary efferent output to target muscles of the forelimb and replacement of the eliminated volitional commands with those imposed by stimulus-evoked activity (Griffin et al. 2011). One mechanism by which volitional cortical commands may be eliminated is by interruption and blockage of afferent input signals to corticospinal neurons resulting from collision between stimulus evoked antidromically conducting spikes and naturally occurring spikes on axons supplying afferent input to the corticospinal neurons. With natural synaptic input eliminated, corticospinal neurons would fire at a rate determined solely by stimulation.

This phenomenon of replacement, or “hijacking,” has been shown to occur in M1 with high-frequency microstimulation (Griffin et al. 2011) as well as in subcortical areas such as the subthalamus with deep brain stimulation (DBS) (Garcia et al. 2005). Interestingly, frequency parameters that have been empirically adopted to therapeutically treat diseases such as Parkinson’s disease with DBS are in the range of 120–180 Hz (Garcia et al. 2005). The similarity in effective frequency ranges used in DBS and the present study likely reflects a common mechanism underlying achievement of the desired behavioral outcome in which neural activity of target cells is replaced with artificial stimulus-evoked activity. Hijacking of corticospinal cell activity by electrical stimulation likely occurs in direct response to application of stimulus frequencies that exceed the natural movement-related firing rates of cortical neurons and afferent inputs (Griffin et al. 2011). The stimulus rates found to be optimal in the present study (80–140 Hz, median 110 Hz) are similar to the expected average maximum firing rates of cortical cells (Capaday et al. 2011) and, therefore, would be expected to be effective in blocking and replacing natural movement-related activity. However, in order to evoke complete movements with stimulation, it is necessary to recruit a sufficient number of corticospinal cells to activate a muscle synergy capable of generating the joint forces needed to move the limb to a new position. Stimulus intensity clearly plays a major role in the number of corticospinal neurons that are activated. The stimulus intensity range found to be effective in producing HFLD-ICMS-evoked translocation of the limb to a new stable end-point position was 80–140 µA with a median intensity of 110 µA. The following equation can be used to calculate the spread of effective stimulus current within the cortex:

\[ r = \sqrt{\frac{i}{k}} \]

where \( r \) is the radius of the stimulus-activated cortical volume, \( i \) is the stimulus intensity, and \( k \) is the current-distance constant. Based on a minimal excitability constant of 250 µA/mm² for the largest cortical neurons or an intermediate excitability of 1,292 µA/mm² (Cheney and Fetz 1985; Tehovnik et al. 2006), the area of directly activated cortical tissue can be estimated to be 1.01–1.76 mm² or 0.20–0.34 mm², respectively. Based on estimates of the density of corticospinal neurons (He et al. 1993) and a minimal excitability constant, this would correspond to activation of 302–528 corticospinal neurons. However, this does not take into account transsynaptic activation via physiological spread of stimulus current, which could be substantial at the HFLD-ICMS frequency ranges used in this study. Therefore, the true number of corticospinal cells activated becomes very difficult to estimate with certainty (Cheney and Fetz 1985).

Effect of stimulus parameters on muscles not directly affected by stimulation. At what level does HFLD-ICMS interfere with the internal motor program underlying voluntary movement? Does HFLD-ICMS hijack only the cortical output mechanism responsible for movement execution, or does it also interfere with “upstream” events involved with motor planning or other higher-level functions? Interference with higher-level functions might occur through antidromic activation of neurons in secondary cortical motor areas as well as thalamic afferent input to M1. If higher-level functions were interrupted by HFLD-ICMS, the effects on movement might extend beyond the muscles directly activated (hijacked) by stimulation, leaving the monkey unable to produce voluntary movements in unaffected parts of the stimulated limb or even more distant body parts. However, we found that muscles not directly affected by stimulation preserve voluntary activity. As a result, the monkey retains voluntary control over these unaffected muscles during stimulation, even for muscles acting on joints adjacent to those controlled by stimulation. For example, when HFLD-ICMS applied to M1 hijacked wrist and digit muscles, the monkey’s ability to activate proximal muscles under voluntary control was preserved. Indeed, in such trials the monkey would often move the unaffected proximal joints in an apparent attempt to reposition the hand near an unclaimed food reward, although the monkey was then unable to use its hand to grasp the food. The reverse was also observed, with loss of voluntary control over proximal muscles due to hijacking but retention of voluntary control over wrist and digit muscles. These findings suggest that HFLD-ICMS acts primarily on the neural circuits responsible for movement execution rather than on upstream processes such as those involved with motivation and movement planning. Alternatively, stimulation antidromically affecting upstream circuits may primarily act on somatotopically similar output circuits as those in M1 to which they project.

Stimulus parameters used in present study compared with those used in previous studies. We found that applying stimulus parameters of 80–140 Hz, 80–140 µA, and 1,000-ms duration (using cathodal biphasic 0.2-ms pulses) was effective for evoking translocation of the forelimb to new stable end-point positions in an awake and behaving monkey. These parameters have similarities to stimulus parameters used in previous studies to evoke prolonged limb movements or eye saccades; however, there are some significant differences. To elicit smooth and stable eye saccades from parietal cortex, parameters of 500 Hz, 100–200 µA, and 100 ms with biphasic pulses of 0.1-ms duration were found to be effective (Thier and Andersen 1998). To evoke limb movements in an anesthetized
cat, parameters of 333 Hz, 10–100 μA, and 500 ms with 0.2-μs pulses were used (Ethier et al. 2006), although these movements did not necessarily meet the criteria applied in our study. For eliciting movements in the monkey forelimb, Graziano et al. (2002) used 200 Hz, 100 μA, and a stimulus train duration of 500 ms with biphasic 0.2-ms pulses. In anesthetized rodents, parameters of 181–400 Hz, 20–75 μA, and train durations of <40 ms using cathodal pulses were found to be effective ranges for eliciting movements (Young et al. 2011), although the goals of that study were somewhat different than ours and did not include evoking complete movements to stable end points. The variability in stimulus parameters used between studies likely also reflects species differences and the use of anesthetizing agents. The stimulus duration used in the present study (1,000 ms) was longer than those used in previous mapping studies because the latency from stimulus onset to arrival of the forelimb at a stable spatial end point had a wide range, with nearly half of the evoked spatial end points exceeding stimulation durations used in previous studies.

**Summary and conclusions.** Our results suggest a range of stimulus parameters applied to M1 of an awake and behaving monkey that are both safe and effective for evoking translocation and subsequent stabilization of the stimulated limb at a spatial end point: 80–140 Hz, 80–140 μA, and 1,000 ms, with a mean spatial end-point time of 475.8 ± 170.9 ms. The mean successful frequency, normalized for all trials recorded in the study, was 117.6 ± 23.2 Hz, and the mean successful intensity was 108.3 ± 24.4 μA. Additionally, for all trials, the median successful stimulus frequency was 110 Hz and the median stimulus intensity was 110 μA. Attenuated parameters resulted in inconsistent, truncated, or undetectable movements, while intensified parameters increased the potential for large-scale physiological spread and adverse focal motor effects. Establishing cortical stimulation parameters that yield consistent stimulus-evoked end points provides a foundation for the systematic and comprehensive mapping of movement space and associated muscle synergies in M1. The results add to our understanding of how the central nervous system encodes movement, and could aid in advancing the application of neuroprosthetic devices.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**


**REFERENCES**


