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Reanimating the arm and hand with intraspinal microstimulation

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Abstract

To date, there is no effective therapy for spinal cord injury, and many patients could benefit dramatically from at least partial restoration of arm and hand function. Despite a substantial body of research investigating intraspinal microstimulation (ISMS) in frogs, rodents and cats, little is known about upper-limb responses to cervical stimulation in the primate. Here, we show for the first time that long trains of ISMS delivered to the macaque spinal cord can evoke functional arm and hand movements. Complex movements involving coordinated activation of multiple muscles could be elicited from a single electrode, while just two electrodes were required for independent control of reaching and grasping. We found that the motor responses to ISMS were described by a dual exponential model that depended only on stimulation history. We demonstrate that this model can be inverted to generate stimulus trains capable of eliciting arbitrary, graded motor responses, and could be used to restore volitional movements in a closed-loop brain-machine interface.

1. Introduction

While functional electrical stimulation (FES) systems targeting muscles and peripheral nerves can generate simple arm and hand movements (Keith 2001, Popovic *et al* 2002), restoring normal function to the paralysed upper limb remains a formidable challenge. Up to 34 muscles act synergistically on the fingers and thumb alone to produce an enormous repertoire of manipulative ability. Many of these muscles are small and inaccessible via surface stimulation, and even extensive subcutaneous implants are problematic since neighbouring muscles act differently on the hand. Furthermore, stimulation of motor nerves produces an inverted recruitment order whereby large fibres are preferentially activated (Prochazka 1993), leading to noisy force production and rapid fatigue.

Pioneering work in the lumbar cord of species including frogs (Bizzi *et al* 1995), rodents (Tresch and Bizzi 1999) and cats (Mushahwar *et al* 2000, Grill and Lemay 2002) has suggested that intraspinal microstimulation (ISMS) may provide a means of artificially eliciting movements that avoids many of the disadvantages of conventional FES. Microampere current delivered to individual sites in the grey matter activates spinal circuitry (Schouenborg 2008) that recruits coordinated patterns of muscle contractions. For example, stimulation of intermediate laminae in the frog spinal cord elicits convergent force fields that act to bring the leg to a particular point in space (Mussa-Ivaldi *et al* 1994). Since

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motoneurons are activated transsynaptically, recruitment order is likely to be normalized and fatigue reduced (Bamford *et al* 2005).

We are investigating whether ISMS in cervical segments of the primate spinal cord can generate functional movements of the upper limb. Although the relative spinal and supraspinal contributions to upper limb control in the primate remain unclear (Lemon 2008), segmental premotor interneurons with divergent projections to motoneurons are modulated with upper limb movements such as wrist flexion/extension (Perlmutter *et al* 1998). Short trains of microstimulation in the cervical cord at near-threshold current often elicit responses in multiple muscles, with co-activation of fingers and thumb flexion being particularly common (Moritz *et al* 2007). These results suggest that cervical ISMS may provide a means to activate coordinated muscle patterns that form the building blocks for functional movements such as reaching and grasping.

We report here a series of experiments in anaesthetized monkeys to test whether longer trains of stimuli delivered to a small number of implanted cervical spinal electrodes can generate functional movements of the upper limb. We first analyse muscle responses to trains of stimuli at fixed frequency, and identify a nonlinear frequency dependence that presumably reflects spinal mechanisms. We show that these results are described by a simple recurrent model, which can be inverted to generate stimulus trains for arbitrary, graded motor output. Finally, we show that stimulation of just two spinal sites can be combined to generate functional reaching and grasping movements. We conclude with a discussion of some advantages and disadvantages of cervical ISMS in the context of developing closed-loop brain-machine interfaces (BMIs) to restore volitional control of the upper limb to paralysed patients.

2. Methods

2.1. Animals and surgical procedures

The experiments were approved by the local ethics committee at Newcastle University and the procedures followed the UK Animals (Scientific Procedures) Act 1986. Experiments were performed on six female rhesus macaque monkeys (*Macaca mulatta*) that had previously been used as breeding animals (monkeys A, S, T, H, O and M; average age: 13.4 years). We include data on responses to muscle and peripheral nerve stimulation under ketamine/dormitor sedation from monkey M. The other monkeys were terminally anaesthetized (induced with ketamine, maintained with isoflourane during surgical dissection, and then switched to an intravenous infusion of propofol/alfentanil to maintain spinal excitability during stimulation experiments). Respiration was supported by artificial ventilation through a tracheotomy and body temperature, blood pressure, blood oxygenation and end-tidal CO₂ were monitored throughout.

Electromyogram (EMG) signals from arm and hand muscles were amplified ($\times 1000$), high-pass filtered at 30 Hz (Neurolog NL824, Digitimer) and sampled at 1 kHz (Power 1401, Cambridge Electronic Design). In three monkeys (A, S and T), we recorded from 16 muscles; in monkey H from five; in monkey O from two; and in monkey M from one muscle.

Motor responses were recorded either as grip force in the hand or as isometric forces and torques at the wrist. To record grip force, a Foley catheter was inflated with air and connected to a pressure sensor. For isometric force recording, the hand of the monkey was fixed into a padded clamshell mounted to a six-axis force/torque transducer.

2.2. Spinal cord stimulation

Access to the cervical spinal cord was gained through a laminectomy of vertebrae C4–T1, and the dura mater was removed. Teflon-insulated tungsten microwires (50 μm diameter, $\sim 100\text{ k}\Omega$ impedance) were inserted 3–6 mm into the cervical spinal cord (on average 10 per animal) targeting the motoneuron pools of the ventral horn. In one animal, a 16-channel Michigan probe was used for stimulation. Since we did not expect to find a significant somatotopy of stimulation effects (Moritz *et al* 2007), we covered the extent of the cervical enlargement between C6 and T1 at lateralities between 1 and 3 mm. Penetration depth was determined by making a sharp bend in the microwire at the appropriate length.

2.3. Stimulation protocols

Stimuli (biphasic, cathodic phase first, 200 μs per phase) were delivered using Model 2100 and Model 2200 isolated stimulators (AM Systems). The data we report here were collected using the following stimulation protocols.

Intensity series—Single stimuli were delivered in pseudo-random order with intensities between 5 and 50 μA in 5 μA increments (ten stimuli per intensity; interstimulus interval (ISI) 500 ms). If no EMG responses were seen, a second series used intensities between 20 and 200 μA in 20 μA increments. Motor threshold was defined as the lowest current required to evoke an EMG response in one muscle with at least 50% probability. For subsequent stimulation protocols, stimulus currents were increased to achieve consistent visible muscle contractions (typically $1.5\times$ to $10\times$ motor threshold).

Frequency series—To investigate the motor response to different stimulation frequencies, we delivered a pseudo-randomized sequence of stimulus trains (15 pulses each) at frequencies from 10 to 100 Hz (in 10 Hz steps) and with a 2 s interval between trains. Each frequency was repeated 20 times in one session.

Regular and long/short interval stimulation—To explore the effect of varying the temporal structure within a stimulus train, we constructed stimulus trains containing 20 stimuli at six average frequencies (20, 22, 25, 29, 33 and 36 Hz) using two methods. In the ‘regular’ condition, successive stimuli in a train were separated by a uniform ISI. In the ‘long/short interval’ conditions, alternate intervals were fixed at 50 ms (in order to maintain a fused contraction), or shortened so as to preserve the same overall duration as in the regular condition (and thus the same average frequency). Note that since the ISI at 20 Hz is 50 ms, there is no difference between regular and long/short interval stimulus trains at this frequency. One stimulation session contained five trials per condition delivered in pseudo-randomized order.

We compared the effects of ISMS with muscle and nerve stimulation using this stimulation paradigm. In one monkey, we performed three stimulation experiments using needle electrodes in hand and forearm muscles (APB, FCR, FDS). In the same monkey, we performed the same experiment using surface electrode median nerve stimulation. Finally, we used another monkey’s median and ulnar nerve cuff implants to deliver these stimulus trains. Thresholds for muscle and nerve stimulation were determined visually, and subsequent stimuli were delivered 20% above threshold.

Constructing stimulus trains to evoke arbitrary motor responses—To test whether arbitrary motor responses can be achieved by ISMS, we constructed stimulus trains that were designed to evoke target force functions (such as sinusoidal patterns). In one condition, the target force function was iteratively integrated until a threshold was exceeded, at which point a stimulus was delivered and the integrator reset. A minimum ISI of 7 ms was

imposed, and the threshold was chosen so as to reach maximum stimulation rate at the maximum of the target function.

In a second condition, we tested whether better results could be achieved when temporal features of the muscle response to stimulation were taken into account. For the same sinusoidal target function, as used above, we employed a ‘muscle response model’, as described in the following section, again forcing a minimum ISI of 7 ms and reaching maximum stimulation rate at target function maximum.

Since the target function was defined in arbitrary units rather than as an absolute force, we then scaled the target function to match the measured motor responses, and R^2 -values were computed.

2.4. Muscle response model

Force responses elicited by single motor unit action potentials have been previously approximated by critically damped second-order systems (Milner-Brown *et al* 1973). Here, following our observations, we assume that this model is also a sufficient approximation for intraspinal stimuli. Accordingly, we assumed a normalized twitch force response to a single stimulus occurring at time zero to have a time course as given by

$$f(t) = \begin{cases} \frac{t}{\tau} \exp\left(1 - \frac{t}{\tau}\right) & t \geq 0 \\ 0 & \text{otherwise,} \end{cases} \quad (1)$$

where τ is the time of the maximum and here assumed to be 50 ms, as this time course was suggested by our initial stimulation experiments. We further assumed that the twitch response amplitude depends on the times of previous stimuli. We then constructed a simple recurrent modulation model with only four parameters consisting of two decaying exponentials:

$$r(t_n) = 1 + \sum_{i=1}^{n-1} \left(p_1 \exp\left(-\frac{t_i}{p_2}\right) + p_3 \exp\left(-\frac{t_i}{p_4}\right) \right). \quad (2)$$

The two exponential terms were introduced in order to capture the facilitation and suppression we observed in response to stimulation at different frequencies.

The frequency series data for muscles that were consistently activated by a given stimulation site were normalized to the first response in a train. We then performed least-squares minimization to fit the model parameters for each stimulation site–muscle pair. Two-thirds of the trials were used to fit the data, allowing the model fit to be tested on the remaining data. R^2 -values were computed for the testing subset. It is worth noting that, since the model in (2) does not necessarily allow a constant solution equal to the mean of the training data, R^2 -values can be negative.

In order to predict the motor response for a stimulus train given by its times $t_1 \dots t_n$, we convolved these stimulus times with the twitch force response from (1) multiplied by the respective amplitude $r(t_i)$ and summed these scaled responses:

$$F(t) = \sum_{i=1}^n r(t_i) \cdot f(t - t_i). \quad (3)$$

Single twitches and their summation are shown in figure 2(b). To construct a stimulus train for evoking a given target motor response, we progressively compared the current force

prediction with the target function in time steps of 1 ms. Whenever the predicted motor response fell below the target function, a stimulus was delivered and the force prediction updated accordingly. Stimulation rates were limited by imposing a minimum ISI of 7 ms.

Although here this method was used to control open-loop stimulation with pre-constructed stimulus trains, it could easily be adapted for closed-loop stimulation since only information about past stimuli and the current target force is used to generate new stimuli. Furthermore, once appropriate parameters have been determined, this algorithm requires minimal computational resources and can be executed in real time.

3. Results

3.1. Dataset

We report data on spinal cord stimulation from six animals, using 46 microwire electrodes and one Michigan probe (monkey A: 14 microwires, monkey H: two, monkey S: nine, monkey T: 21, and one Michigan probe in monkey O). We determined motor threshold for 40 microwires, with an average threshold of $63 \mu\text{A}$ (s.d. $55 \mu\text{A}$). On average, stimulation evoked EMG responses in 2.5 (s.d. 1.6) muscles at threshold. The remaining six microwires did not show stimulation effects up to $200 \mu\text{A}$.

We then performed stimulation experiments using the protocols described above. Frequency response data were acquired from 24 stimulation electrodes, yielding 346 site–muscle combinations for analysis. Of these sites, 17 elicited reliable EMG responses in at least one muscle throughout the recording (90 site–muscle combinations). For long/short interval stimulation, data were collected from nine spinal sites of monkeys A, H, O and S; three peripheral nerves (median and ulnar nerves of monkey O, median nerve of monkey M); and three muscles of monkey M.

3.2. Frequency dependence of muscle responses evoked by ISMS trains

Rectified EMG responses for trains of 15 intraspinal stimuli at different frequencies are shown in figure 1. Of those stimulation site–muscle combinations with a consistent EMG response (90), about half showed rapid overall suppression after only a few stimuli (averaged data shown in figure 1(d)). Another 18/90 pairs showed facilitation for the first few high-frequency stimuli and then suppression (figure 1(c)). The third large group showed strong facilitation for high-frequency stimulation that lasted for the entire duration of the stimulation trains (15/90 pairs; cf figure 1(b)). The remaining stimulation site–muscle combinations (17) showed more complex response patterns that were not easily classified. In many cases, a single stimulation electrode contributed to more than one class of response in combination with different muscles.

We then fitted the parameters for the muscle response model (2) for every stimulation site–muscle combination that fell into one of these categories. The best fit for a site–muscle combination typically consisted of a sum of positive and negative decaying exponentials. The time constants of these decaying exponentials (p_2 and p_4 in 2) were in the range of 50–200 ms. For the groups showing high-frequency facilitation, the time constant for the negative exponential was usually larger than the one for the positive, yielding recurrent modulation functions schematically shown in figure 2(a).

The mean R^2 -value for these fits was 0.37 (s.d. 0.29). We also used the average data from each response group to fit the recurrent modulation function. The respective model predictions are shown in figures 1(e)–(g), and the group R^2 -values were 0.88, 0.87 and 0.86, respectively.

3.3. Long/short interval stimulation of the spinal cord elicits stronger muscle contractions than regular stimulation

From the observation that many stimulation sites showed facilitated EMG responses to high-frequency stimulation, we speculated that stimulation trains containing high-frequency components might prove to be a more efficient method to generate force compared to regular trains of the same average frequency. By limiting the maximum ISI in the long/short trains (to 50 ms), a fused contraction can be maintained while the shorter interval can evoke temporal facilitation. To determine the locus of facilitation, we also delivered equivalent stimulus trains directly to muscles and peripheral nerves. We compared motor responses measured either as grip pressure or as isometric forces of the wrist resulting from regular and long/short interval stimulation trains of increasing average frequency. Stimulus amplitudes were on average 144 μA for ISMS, 3.3 mA for nerve stimulation and 1.4 mA for muscle stimulation. Absolute force values recorded varied within stimulation site groups by as much as an order of magnitude, but on average were comparable across groups. This variation can be partially accounted for by the effectiveness with which different muscles activated by stimulation contributed to forces we could measure at the wrist or hand. In figure 3(a), sample responses to a 20 Hz stimulus train and for regular and long/short 36 Hz conditions are shown. Measured motor responses were averaged across trials and normalized by the response to 20 Hz stimulation.

Panel (b) compiles these results for spinal cord, peripheral nerve and muscle stimulation experiments across animals and stimulation sites. For spinal cord, nerve and muscle stimulation, average force increased with frequency. However, the slope of this increase is stronger in the spinal cord than for other stimulation targets. Furthermore, only in the spinal cord was there a significant difference between regular and long/short stimulus trains ($p < 0.05$). This shows that by varying the temporal pattern of spinal stimulation it is possible to increase the amount of force generated by a given number of stimuli, whilst preserving a fused contraction of the muscles. Therefore, temporal facilitation within the spinal cord provides opportunities for efficient activation of muscles with a minimal number of stimuli.

3.4. Graded motor responses produced by ISMS

We compared the ability of stimulus trains constructed using two methods (integrate-and-fire and muscle response model; see section 2) to produce arbitrary, graded target motor responses. In this example, we chose stimulation sites that reliably produced grasp movements and used a sinusoidal target grip force profile. While both stimulation methods produced graded responses of similar amplitude (figure 4), the muscle response model achieved a slightly better match to the target function than the integrate-and-fire method ($R^2 = 0.96$ and $R^2 = 0.92$ for averaged trials, respectively). We found that a range of motor response patterns could be elicited using this method, including both phasic and tonic contractions, and we could accurately control both grasping and arm movements. Although here stimulus trains were calculated in advance for predetermined target forces and delivered in an open-loop manner, in principle this method could be applied to target functions generated in real time, for example, decoded from cortical activity by closed-loop BMIs.

3.5. Functional, independent reaching and grasping movements generated by ISMS

Figure 5 illustrates two typical responses elicited by ISMS and demonstrates that they could be combined into functional movements (supplementary movie available at stacks.iop.org/JNE/8/054001/mmedia).

In this example, the first stimulation site produced elbow extension, and the second mainly finger and wrist flexion (figure 5(a)). After onset transients, stimulation for several seconds

repeatedly produced steady EMG responses and movements. Note also that the motor responses elicited by each stimulation channel were in this case largely independent of the stimulation delivered to the other channel. Therefore, both movement components could be activated independently, enabling the limb to grasp, transport and release an object, as shown in figures 5(b)–(g).

4. Discussion

This is the first study to investigate the upper-limb muscle activity and movements elicited by long trains of microstimulation in the cervical spinal cord of primates. We find that stimulation through a small number of electrodes can produce functional movements, including reaching and grasping, that involve co-ordination of multiple muscles. EMG responses show a mixed pattern of temporal facilitation and suppression that can be reasonably approximated by a simple dual exponential model. The advantage of this model is that it can be inverted to construct on-line stimulus trains that produce arbitrary, graded force profiles. Such an approach is in principle applicable in BMI paradigms where the desired force profile would be decoded in real time from cortical activity. Therefore, a relatively simple connection from cortex to spinal cord may provide a means to restore volitional movements of the paralysed limb. Such a connection could be implemented by an autonomous electronic device equipped with simple recording and stimulation capabilities (Jackson *et al* 2006).

In the present study, we have not addressed the neural mechanisms by which movements are produced. Stimulation could act directly by depolarizing motoneuron cell bodies and initial segments, as well as indirectly via afferent fibres, descending pathways and local intraspinal circuits. We see a nonlinear frequency dependence of the muscle response to ISMS, in contrast to direct stimulation of the motor nerves, and although we cannot rule out a contribution from intrinsic mechanisms such as persistent inward currents or slow after hyperpolarization (Eken *et al* 1989), it is likely that nonlinear synaptic interactions within the spinal cord are involved and include both excitatory and inhibitory influences. Previous studies have suggested that fibres may have lower stimulation thresholds than cell bodies (Gustafsson and Jankowska 1976, Histed *et al* 2009) and that afferent fibres are activated at lower intensities than efferent fibres (Gaunt *et al* 2006). However, with trains of supra-threshold stimulation it is likely that all of these components contribute to the movements we observe. Nevertheless, the functional organization of descending projections, reflex pathways and segmental inputs to motoneurons may explain the naturalistic movements involving multiple muscles that we observe from stimulation at a single site. Exploiting these transsynaptic pathways to motoneurons has the additional advantage that a more natural recruitment order may be obtained (Mushahwar and Horch 2000, Bamford *et al* 2005).

An important caveat is that these experiments were performed under general anaesthesia, which is difficult to compare directly to an injured spinal cord. Aoyagi *et al* (2004) have found that ISMS responses can vary between the anaesthetized and decerebrate states. We deliberately chose an anaesthetic regime with minimal effect on spinal cord excitability; nevertheless, further experiments using chronic implants will be required to extend these results to the awake animal. The situation after spinal cord injury is further complicated by plastic changes leading to hyperreflexia and spasticity. Nevertheless, it is possible that artificially restoring naturalistic patterns of activity to spinal circuits through ISMS may help to reduce the detrimental plasticity that results from depriving motoneurons of descending input.

The use of BMI techniques to deliver closed-loop stimulation has received increasing interest in recent years. Two groups have already demonstrated closed-loop cortical control of muscle stimulation in primates to restore upper-limb function (Moritz *et al* 2008, Pohlmeier *et al* 2009). However, the cortex generates muscle contractions only by acting through the spinal cord, so cortical control of ISMS may provide a more intuitive neural prosthesis. An additional advantage of ISMS is the small number of stimulation channels required to control coordinated movements involving multiple muscles. Motor primitives hard-wired into spinal circuits have been postulated as a near-optimal solution to the dimensionality reduction problem that the brain must solve to control natural movements (Mussa-Ivaldi and Bizzi 2000). If so, then by exploiting these same primitives, ISMS may provide a low-dimensional control space that is well suited to restore naturalistic movements. In any case, such stimulation is better suited to implementation in implantable or portable electronics that can operate autonomously (Jackson *et al* 2006). This has the added advantage that continued operation provides greater opportunity for subjects to learn to incorporate artificial connections into their natural motor behaviour. Finally, re-establishing a causal relationship between cortical and spinal neurons may induce activity-dependent plasticity in surviving pathways (Jackson *et al* 2006) with potential application in the rehabilitation of patients with incomplete spinal injuries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Muscle responses to ISMS. (a) Example rectified EMG responses from muscle *abductor digiti minimi* (ADM) to trains of 15 stimuli delivered at 10 Hz (top) and 100 Hz (bottom). Individual traces are shown in grey and the average in black. Stimuli indicated by marks. (b)–(d) Three common types of frequency response patterns. Rectified EMG was normalized by the response to the first stimulus before averaging across trials and stimulation site–muscle combinations. Response to the n th stimulus is shown along the x -axis and stimulation frequency along the y -axis. (b) Response increases for higher frequencies and remains constant for low rates (15/90 stimulation site–muscle pairs), (c) initial facilitation for high frequencies, then suppression (18/90), (d) general suppression for frequencies over 10 Hz (40/90). (e)–(g) Predicted responses using the model given in (2), with parameters fitted to data shown in panels (b)–(d). R^2 -values for the fits are 0.88, 0.87 and 0.86, respectively.

Figure 2.

(a) Dual exponential model of recurrent facilitation/suppression with parameters from example fits shown in figure 1. Red: high-frequency facilitation (cf figure 1(b)); grey: mixed facilitation/suppression (cf figure 1(c)); blue: overall suppression (cf figure 1(d)). (b) Illustration of the stimulus train construction process. Whenever the force prediction (red) falls below the target (blue), a stimulus (black mark) is delivered and the prediction updated. The amplitude of a twitch response is modulated by prior stimuli according to (2). Individual twitch responses are shown in *grey*, the dashed line represents the amplitude of the first response as a reference.

Figure 3.

Motor response to regular and long/short interval stimulation trains delivered to the spinal cord, peripheral nerve or muscle. Conditions were either regular trains of 20 stimuli delivered at 20, 22, 25, 29, 33, 36 Hz, or trains of the same duration and number of stimuli, with alternate ISI fixed at 50 ms or shortened to preserve average frequency (long/short interval condition). (a) Sample force trajectories for the 20 Hz baseline (left, stimuli are identical in regular and long/short conditions), 36 Hz regular (centre) and long/short (right) conditions. Individual trials are shown in grey and the average across trials in black. Stimuli were delivered at marks. (b) Average forces generated during stimulation of the spinal cord (left), peripheral nerve (centre) and muscles (right). Average forces were normalized by the response to 20 Hz stimulation. The asterisks mark conditions for which long/short stimulation trains caused significantly stronger forces than regular trains ($p < 0.05$). Error bars: s.e.m.

Figure 4.

Grip force resulting from stimulus trains constructed with sinusoidal target functions. The upper panel shows the result for stimulus trains produced by the integrate-and-fire method; the lower panel shows trains produced by the muscle response model (see section 2). $R^2 = 0.92$ and $R^2 = 0.96$, respectively.

Figure 5.

Stimulation at two sites in the cervical spinal cord produced grasp and elbow extension movements in an anaesthetized macaque monkey (see also supplementary movie available at stacks.iop.org/JNE/8/054001/mmedia). Stimulation trains consisted of 50 Hz trains that were individually switched on and off by the experimenter. A squash ball was transported from the extended to the flexed position and released. (a) Rectified and low-pass filtered EMG traces for *flexor carpi radialis* (FCR) and *triceps brachii* muscles. Stimulation (50 Hz) on each channel is indicated by bars above the graph. (b)–(g) Video stills of upper limb at times indicated by triangles below panel (a). The background has been removed for visual clarity. Time is given in seconds from first still.