Modularity of Motor Output Evoked By Intraspinal Microstimulation in Cats

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Submitted 11 March 2003; accepted in final form 25 September 2003

Lemay, Michel A. and Warren M. Grill. Modularity of motor output evoked by intraspinal microstimulation in cats. J Neurophysiol 91: 502–514, 2004. First published October 1, 2003; 10.1152/jn.00235.2003. We studied the forces produced at the cat’s hindpaw by microstimulation of the ipsi- and contralateral lumbar spinal cord in spinal intact α-chloralose anesthetized (n = 3) or decerebrate (n = 3) animals. Isometric force and EMG responses were measured at 9–12 limb configurations, with the paw attached to a force transducer and with the hip and femur fixed. The active forces elicited at different limb configurations were summarized as force fields representing the sagittal plane component of the forces produced at the paw throughout the workspace. The forces varied in amplitude over time but the orientations were stable, and the pattern of an active force field was invariant through time. The active force fields divided into four distinct types, and a few of the fields showed convergence to an equilibrium point. The fields were generally produced by coactivation of the hindlimb muscles. In addition, some of the fields were consistent with known spinal reflexes and the stimulation sites producing them were in laminae where the interneurons associated with those reflexes are known to be located. Muscle activation produced by intraspinal stimulation, as assessed by intramuscular EMG activity, was modified with limb configuration, suggesting that the responses were not fixed, but were modified by position-dependent sensory feedback. The force responses may represent basic outputs of the spinal circuitry and may be related to similar spinal primitives found in the frog and rat.

INTRODUCTION

Studies of motor behavior have shown that a large repertoire of coordinated movements are organized at the level of the spinal cord and can be generated independently of higher centers. For example, functional reflexes in the spinal cat can be evoked via natural or electrical stimulation of afferents (e.g., the flexion withdrawal reflex) (Sherrington 1910), and spinal animals can locomote and produce functional reaching movements (reviewed in Grillner 1981; Rossignol 1996). These movements originate from spinal neural circuits and involve proprioceptive and cutaneous afferents as well as various populations of spinal interneurons. A number of the interneurons participating in these reflexes have been identified via anatomical and electrophysiological investigations (Jankowska 1992), and while there appears to be some somatotopy in the locations of interneurons involved in hindlimb reflex behaviors (Levinsson et al. 1999, 2002; Tresch and Bizzi 1999), a number of interneuron types share the same laminar level and rostrocaudal distribution. Thus it has been difficult to establish a relationship between the organization of spinal neurons and the motor behaviors that they mediate.

Despite its shortcomings, including the difficulty in activating specific groups of neurons and the potential ambiguity of the stimulated elements, intraspinal microstimulation has proven a fruitful approach to establish a link between the organization of the spinal cord and naturally and electrically evoked motor behaviors (Giszter et al. 2001). Intraspinal microstimulation of the lumbar spinal cord in frogs, rats, and cats produces functional reflex-like motor responses. In spinal frogs and rats, intraspinal microstimulation produces a limited repertoire of stereotyped motor responses (Giszter et al. 1993; Tresch and Bizzi 1999), and the characteristics of these responses are analogous to reflex responses evoked by peripheral activation of sensory inputs. Similarly, iontophoresis of NMDA into the gray matter of the rostral lumbar spinal cord of spinal frogs produced cyclic motor responses in sequences appropriate for swimming (Saltiel et al. 1998). In cats, studies of intraspinal microstimulation have concentrated on limb kinematic responses, muscle activation, or single joint torques with stimulation delivered in the ventral portion (ventral lamina VII and laminae VIII–IX) of the gray matter (Mushahwar and Horch 2000a,b; Mushahwar et al. 2000, 2002; Stein et al. 2002; Tai et al. 1999, 2000a,b).

This study reports on the isometric forces measured throughout the hindlimb’s workspace in response to microstimulation of the cat lumbar spinal gray at depths ranging from lamina I through the ventral root exit. We quantified the modularity of the force patterns produced at the paw by intraspinal microstimulation and demonstrate that, similar to the frog and rat, intraspinal microstimulation in the cat produced a limited repertoire of stereotyped motor responses. We also quantified the modulation of muscle activation over the limb workspace and demonstrate that, close to the borders of the examined space, the EMG of hindlimb muscles is modulated. These results suggest that position-dependent sensory feedback modifies the motor responses evoked by intraspinal stimulation.

METHODS

Surgical preparation

Results from six adult male cats (domestic short hair, 2.3–3.7 kg) are reported in this study. All animal care and procedures were according to National Institutes of Health guidelines and were reviewed and approved by the Institutional Animal Care and Use Committee of Case Western Reserve University.

All animals were initially anesthetized using ketamine HCl (Ketaset, 15–30 mg/kg, im) given in combination with atropine sulfate (0.05 mg/kg, im). The animals were intubated and maintained at a surgical level of anesthesia with either halothane (0.5–2% in O2, n =
3) or α-chloralose (initial dose of 60 mg/kg iv, supplemented at 15 mg/kg, n = 3). The cephalic vein was catheterized to administer fluid/drugs during the procedure. Animals were ventilated to maintain expired CO$_2$ at 3–4%, body temperature was maintained between 37° and 39°C using thermal pads, warm 0.9% saline with 8.4 mg/ml sodium bicarbonate and 5% dextrose added was administered intra-venously (10–15 ml/kg/h), and carotid blood pressure was monitored throughout the experiment.

A dorsal laminectomy was made from L$_4$–L$_7$ to expose the lumbarosacral spinal cord and spinal roots. Dexamethasone (2 mg/kg, iv) was administered at the completion of the laminectomy and every 6 h thereafter to reduce edema in the spinal cord. The contralateral limb (left) was denervated by transecting the sciatic, femoral and obturator nerves. This denervation was performed to prevent mechanical coupling (through the pelvis) of the contralateral limb’s response to the force sensor on which the ipsilateral limb was attached. The EMG activity of four hindlimb muscles was monitored using fine bifilar electrodes inserted into four hindlimb muscles: knee flexor (biceps femoris or semimembranosus), knee extensor (vastus lateralis), ankle extensor (medial or lateral gastrocnemius), and flexor (tibialis anterior or extensor digitorum longus). The locations of EMG electrodes were verified via postmortem dissection. Electrodes were inserted approxi-mately midway between the hip and the knee into the vastus lateralis and posterior to the femur approximately midway between the hip and the knee into the biceps femoris or semimembranosus. Stimulation through the electrodes was used to confirm that activation produced the correct mechanical action.

Following implantation of the EMG electrodes, the animal was transferred to a stereotaxic frame. The head and spinal vertebrae (L$_3$ and S$_2$) were clamped and fixed into the frame. The animal’s pelvis and femur were held with bone pins, with the pelvis and femur held in the normal stance orientations, i.e., pelvis angle was ≈110° with respect to horizontal (counterclockwise rotation), and the angle between the hip and pelvis was ≈110° (Fig. 1). The paw of the right hindlimb (hindlimb ipsilateral to the spinal stimulation side) was attached to a small bar by compressing the plantar surface of the paw to the bar with a custom cast covering the foot and tightened to the bar with tie-wraps. The bar itself was mounted on a six-axis force transducer (nano17, ATI Industrial Automation) by a rotational joint. The force transducer was mounted on a railing system that allowed positioning of the force sensor throughout the workspace of the lower leg and paw, while the rotational joint permitted sagittal plane rotation of the ankle and thus changes in the knee and ankle joint angles as the limb endpoint was moved.

Once the animal was securely mounted in the frame, a decerebra- tion was performed in the animals prepared under halothane anesthesia. The bone over the occipital and parietal lobes was removed. The carotid arteries were ligated, and the brain stem was transected just rostral to the superior colliculi and continuing rostroventrally to a point caudal to the mammillary bodies, producing a mesencephalic or postmammillary preparation. The brain rostral to the transection was removed (including cortex and thalamus) and the skull packed with Surgicel, Avitene, and agar to control bleeding. Dextan was administered if needed to maintain blood pressure, and anesthesia was discontinued once the decerebration was completed. The dura was opened to allow identification of the spinal roots, and the spinal cord was bathed in warm mineral oil.

Data collection

Motor responses were elicited by intraspinal microstimulation with trains of biphasic current pulses (train duration: 0.5 s, frequency: 40 Hz, pulse duration: 100 μs, pulse amplitude: 50–100 μA) delivered via iridium wire microelectrodes (50 μm diam; IS-300, Huntington Medical Research Institutes). Endpoint forces evoked by stimulation along dorsal to ventral penetrations were measured at depth increments of 200 μm, at a series of positions spanning L$_4$–L$_7$ rostrocaudally and from the medial to lateral gray matter. At selected depths along each penetration, the limb was moved to nine different locations on a 6 × 6 cm grid (or 12 positions on a 9 × 6 cm grid) centered on a mid-stance position, and responses were evoked at each location while stimulation parameters and electrode position were kept constant. The workspace covered by our grid was about three times the step height and one-quarter of the step length of an average size cat, and the changes in ankle and knee joint angles spanned those encountered during locomotion (Fig. 1). The isometric forces produced at the paw were sampled at 2,500 Hz, and the raw EMG signals were amplified, filtered (10–1,000 Hz), displayed, and sampled at 2,500 Hz. To ensure that forces were stable over time, we repeated the force measurement at the mid-stance position after forces at the other eight grid positions were collected. Responses were stable during the collection of force fields, and the force vectors at mid-stance before and after the measurement of forces at other positions differed by 9° (SD) in direction and 0.13 ± 0.71 (SD) N in magnitude (n = 67 sets of force measurements over the grid).

At the completion of the spinal mapping experiments, we also measured the forces produced by stimulation of single hindlimb muscles in three animals. The muscles were activated with trains of biphasic current pulses (train duration: 0.5 s, frequency: 40 Hz, pulse duration: 100 μs, pulse amplitude: 1–4 mA) delivered through the EMG electrodes implanted in each muscle. Ten single muscle force fields were measured: two tibialis anterior, two biceps femoris, three vastus lateralis, two medial gastrocnemius, and one semimembranosus. All the muscles studied produce forces above ≈0.2 N with pulse amplitudes of 4 mA or less. Forces were again measured at 9–12 points on the grid centered on the mid-stance position while stimulation parameters were kept constant.

**Force field reconstruction**

The forces measured at 9–12 locations of the paw endpoint were used to calculate the forces acting on the endpoint throughout the workspace. The endpoint forces measured in the sagittal plane were represented as two-dimensional vectors (3rd axis of the force vector was discarded), and fields representing the force vector orientations and magnitudes throughout the workspace were constructed (Fig. 1). The workspace was divided into triangles, and the forces within a triangle were calculated by linear interpolation based on the force vectors measured at the vertices of the triangle. The forces at each corner of each triangle yielded one force vector ($F_x$, $F_y$), as well as one position ($x$, $y$) coordinate. Combining the three corners of a triangle yielded six unknowns and six equations.

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**FIG. 1.** Construction of a field force from measurement of isometric force vectors at the endpoint of the limb. **Left:** with the femur held fixed via pins, the endpoint was moved on a 3 × 3 cm grid where the dots indicate the spatial locations where forces were recorded. Thin lines indicate orientation of the limb at different endpoint positions. **Right:** measured force vectors (thick dark arrows), triangles dividing the workspace, and the interpolated force vectors (thin light arrows). Forces represented are total forces evoked by intraspinal microstimulation (active and passive) minus forces due to gravity. The field exhibited convergence, i.e., net endpoint forces went to 0 at a location in the workspace indicated by the black circle.
previous equations, with a triangle’s corners. Forces within a triangle were estimated by using the $a_{ij}$ parameters associated with that triangle, as in Fig. 1. We constructed our triangulation to minimize the distance between the interpolated points and the triangle vertices.

The forces were divided into a passive component (forces measured before the onset of stimulation and due to gravity and limb passive properties), and an active component (total force during stimulation minus the passive force). The total, active, and passive force fields were reconstructed, but the analyses are concerned principally with the active fields.

**Force pattern classification**

We divided the active force patterns obtained with intraspinal microstimulation into groups using cluster analysis methods. Cluster analysis partitions a set of objects into a number of disjoint groups so as to optimize a mathematical criterion. In this instance, we used the squared Euclidean distance between cases as our partitioning criteria. A case was defined as the set of forces at each of the nine positions for each of the muscles produces a vector, and the relative activation levels and biomechanical properties of muscles were responsible for producing the observed force patterns.

The split-half Spearman correlation coefficient was used to verify our stereotaxic measurements. At the completion of each experiment, the spinal cord was fixed in situ by immersion in 10% buffered formalin solution for approximately 30 min. The spinal cord was then excised and fixed for 2–3 days in refrigerated 10% buffered formalin solution. The cord was blocked in segments, frozen, serially sectioned in the transverse plane, and stained with cresyl violet (Histo Techniques, Powell, OH). The sections were examined microscopically to establish the medio-lateral and dorso-ventral locations of our stimulation sites. Using our stereotaxic measurements, and sections from the matching segment of the animal’s spinal cord, we established the laminar location for each stimulation site.

**EMG analysis and processing**

Correlations between the type of endpoint force pattern and the pattern of active muscles were investigated using multinomial logistic regression analysis. This analysis examined the relationship between a categorical dependent variable (force pattern type) and a set of categorical predictor variables (active muscles for each force pattern). Results are interpreted similarly as for a regression analysis with categorical predictor variables (active muscles for each force pattern).

The EMGs were rectified and averaged over 10-ms bins. Normalized relative amplitude bins for each muscle were constructed by dividing binned EMG for that muscle at each endpoint position by the sum of the maximum binned EMGs of all muscles at that endpoint position irrespective of time (i.e., the maxima were not taken at one time point but each endpoint position was normalized separately from the others). These normalized bins ranged from 0 to 1 and described the relative amplitude of each muscle’s EMG with respect to the total EMG signal over time (see Fig. 9).

In addition, the normalized binned EMGs were analyzed to determine which of two hypotheses best described the relationship between muscle activation and limb configuration. The first hypothesis assumed that the activation of muscles produced by intraspinal microstimulation was best described as a feedforward control system. Under that hypothesis, the activation level of each muscle was invariant with position, and the relative activation levels and biomechanical properties of muscles were responsible for producing the observed force patterns. The second hypothesis assumed that the activation of muscles produced by intraspinal microstimulation was best described as a feedback control system. Under that hypothesis, the activation level of each or some of the muscles varied with position, and the observed force patterns were the result of sensory feedback in addition to the intrinsic biomechanical properties.

The complete EMG vector (a vector formed by concatenating the normalized binned EMGs of each of the individual muscles for an endpoint position) was analyzed across the workspace positions (see Fig. 9). The concatenated EMG vector at each position formed a case, and clustering methods were used to determine if the patterns of normalized EMGs were of a single form across all endpoint positions or if they varied with endpoint position. This analysis was chosen over one examining the amplitude of the EMGs because the time pattern of EMGs is consistent during contractions for bilateral intramuscular electrodes in different locations in the muscle, while amplitude varies greatly with the electrode location within the muscle (Morris et al. 1998). Changes in the temporal patterns of EMGs with changes in limb position are therefore indicative of changes in activation rather than position-dependent changes in the electrode pick-up of the EMG signal.

The concatenated EMG vector was clustered with respect to position (each position forming a case) using the squared Euclidean distance between cases as the measure of dissimilarity. Two methods of hierarchical clustering were used to divide the cases: the average linkage (incremental sum of squares). Normalized EMGs whose maximum amplitude were <0.1 were excluded from the analysis, since their contributions were considered minimal. EMGs from muscles spontaneously active were also excluded. These criteria excluded the EMG patterns of 6 of the 67 force field measurements; the remaining 61 EMG patterns had from one to four muscles that met the above amplitude criteria; 15 patterns had one muscle, 20 had two muscles, 21 had three muscles, and 5 had four muscles.

For concatenated EMG vectors that divided into ≥2 clusters with both clustering methods and were formed by joining two or more muscles, we performed a subsequent cluster analysis to examine position-dependent changes in the temporal pattern of the individual muscles’ EMGs. The EMG of each muscle was first normalized individually by its maximum at each position, thereby removing all changes in EMG amplitude due to changes in position. Cluster analysis was applied to the normalized EMGs to determine whether there were changes in the pattern of EMG of individual muscles across positions.

**Spinal tissue processing**

During the course of the experiment, electrodes were cut and left in place at a number of locations in the spinal cord to act as markers that were used to verify our stereotaxic measurements. At the completion of each experiment, the spinal cord was fixed in situ by immersion in 10% buffered formalin solution for approximately 30 min. The spinal cord was then excised and fixed for 2–3 days in refrigerated 10% buffered formalin solution. The cords were blocked in segments, frozen, serially sectioned in the transverse plane, and stained with cresyl violet (Histo Techniques, Powell, OH). The sections were examined microscopically to establish the medio-lateral and dorso-ventral locations of our stimulation sites. Using our stereotaxic measurements, and sections from the matching segment of the animal’s spinal cord, we established the laminar location for each stimulation site.
site. A tissue shrinkage factor of 15% was assumed (Agnew et al. 1993) in localizing the lamina, and the validity of this factor was verified by measuring distances between identified electrode tracks.

RESULTS

Summary

The forces evoked at the endpoint of the hindlimb by intraspinal microstimulation were measured in six animals: three anesthetized with α-chloralose and three decerebrate. Measurements were obtained across 39 penetrations, 26 ipsilateral to the limb and 13 contralateral. Depth was sampled from the dorsal surface to approximately 4,000 μm, although a number of responses were measured at deeper locations. Force patterns were measured at the sites along a penetration that produced stable force vector with repeated stimulation and over a range of depth of approximately 600 μm. We report on the active forces produced by intraspinal microstimulation. Differences were found in the activation thresholds and duration of evoked activity in certain cases (e.g., Fig. 2, bottom) between the anesthetized and decerebrate cats. The force patterns and other characteristics of the force vector over time (besides duration) were similar for both preparations, and the results from both sets of animals were pooled together. Responses observed after the cessation of the stimulus train (off-responses) in the decerebrate preparations were not included in the analyses.

Force vector time course

Microstimulation of the lumbar spinal cord produced forces at the paw only during the stimulation train in the cats anesthetized with α-chloralose, while in the decerebrate cats, the evoked forces, in some instances, outlasted the stimulation. Figure 2 shows examples of the active force vectors in the

![Diagram of force vectors](image_url)
sagittal plane at selected depths and throughout time for two microelectrode tracks in two animals. The track on the left was obtained in an anesthetized animal and was localized in the L₅ segment 1,550 μm ipsilateral from the midline. The track on the right was obtained in a decerebrate animal and was also localized in the L₅ segment, 1,700 μm ipsilateral from the midline. The orientation of the force vectors evoked by stimulation was consistent during the stimulation train at each depth and consistent across changes in depth of 400–800 μm. On average, the force response along a penetration maintained a consistent orientation (±8° on average for 64 tracks with more than 1 depth) over a depth of 1,046 ± 449 μm (n = 48 sites with the responsive region of the track bounded by 2 regions producing no force). The latency between stimulation onset and force onset was 50–100 ms, which was typical of the latencies observed. Forces in the decerebrate animals were often maintained for several seconds beyond the end of the stimulation period as shown for the track on the right of Fig. 2 at shallow depths of penetration.

For the track in the anesthetized animal, stimulation over three depth ranges evoked distinct force patterns. Two of the force patterns were flexion responses, while the third was a rostral extension response (more on force pattern types in Force pattern types). The first flexion response was observed between the surface and 800 μm; the second flexion response was observed starting at a depth of 2,000 μm, and this response subsided at 3,800 μm. Note that the force vector rotated rostrally between 2,800 and 3,600 μm, which may indicate that a rostral flexion response, as opposed to a caudal flexion response, was activated at the deeper point, but we did not measure a field at that depth. Finally, a rostral extension response was observed over the 4,400- to 4,600-μm depth range. This penetration was not pursued deeper than 4,600 μm.

Similar results were observed for the track in the decerebrate animal: stimulation over three depth ranges produced distinct force patterns. A flexion response was observed at shallow depths of penetration (0–1,200 μm), and two caudal extension responses were observed at 3,200–3,400 and 4,200–4,800 μm. The force vector orientation within a depth range producing a distinct force was more consistent for this track, and a single type of force vector was observed over each depth range.

Force pattern types

The patterns of endpoint forces ("force fields") obtained by intraspinal microstimulation at 67 different sites in six animals were, by visual inspection, considered to be of four types: caudal flexion (CF) responses that pulled the limb toward the body, caudal extensors (CE) that extended the limb backward, rostral extensors (RE) that extended the limb forward, and one rostral flexor (RF) that flexed the limb forward (Fig. 3). This grouping was confirmed by a cluster analysis of the 67 fields. The average linkage between groups was used to cluster the field types with the dissimilarity measure equal to the squared Euclidean distances. The dissimilarity matrix from the sorted dendrogram is depicted in Fig. 5 to illustrate further the validity of the grouping of endpoint force responses into four types. The matrix of the squared Euclidean distances was sorted based on the dendrogram output so that fields in the same cluster were adjacent to one another in rows and columns. Lighter squares indicate smaller distances, while darker squares indicate larger distances. The lighter squares along the diagonal represent clusters. The CF responses occupy the largest square, while the RF response occupies a single square.

Representative examples of the active force patterns evoked by single muscle stimulation are presented in Fig. 6. The force
patterns resembled the patterns produced by intraspinal microstimulation, namely the CF, CE, and RE, but none of the active force pattern produced a point of convergence where the endpoint force was equal to zero (4 of the 10 total muscle fields presented an equilibrium point within the workspace due to the flexion action balancing gravity force). Intraspinal stimulation resulted in active force responses that were convergent to an equilibrium point (zero force) within the measured workspace in 3/67 fields (4.5%) and total force responses that were convergent to an equilibrium point within the measured workspace in 15/67 fields (22%). One of the convergent active responses was a CF response evoked by ipsilateral stimulation, while the other two were RE responses evoked by contralateral stimulation. In a biomechanical model study of the cat’s hindlimb, single muscle activation of 32 of the hindlimb muscles never produced points of zero net force in the active field, and muscle co-activation was needed to produce convergence in the active force patterns (Lemay et al. 2002).

Distribution of stimulation sites

The locations of the spinal sites at which fields were measured are reported per spinal segment and are shown in Fig. 7 for the L5, L6, and L7 segments. Most stimulation locations were within the spinal gray matter, with a minority of sites (14 of 67) in the white matter. Stimulation was generally delivered by 10.220.33.1 on April 18, 2017 http://jn.physiology.org/ Downloaded from

![Dendrogram of the grouping of force patterns evoked by intraspinal microstimulation. Patterns were grouped starting with the closest neighbor, and the rescaled distance cluster combine indicates the distance between the groups joined. Groupings are indicated on the left as CF (caudal flexion), RF (rostral flexion), RE (rostral extensor), and CE (caudal extensor).](http://jn.physiology.org/)

![Dissimilarity matrix of grouping of endpoint force patterns from the sorted dendrogram. Matrix of the squared Euclidean distance was sorted based on the dendrogram output so that fields in the same cluster are adjacent to one another in rows and columns. Case number 0 in the sorted output would therefore correspond to case 51 in the dendrogram output, while case 67 corresponds to case 43 (last case) in the dendrogram. Lighter squares indicate smaller distances, while darker squares indicate larger distances. Lighter squares along the diagonal represent clusters. Caudal flexion responses extend from cases 0–34, rostral flexion is represented by a single square, rostral extensions extend from cases 36–45, and caudal extensions extend from cases 46–68. Note how the caudal extensor square along the diagonal is composed of 2 squares corresponding to 2 subgroups [(2–48) and (24–43)] on the dendrogram of Fig. 4, and similarly for the caudal flexion square being formed by 2 squares corresponding to 2 subgroups [(51–15) and (45–58)] on the dendrogram of Fig. 4.](http://jn.physiology.org/)

<table>
<thead>
<tr>
<th>Stim Side</th>
<th>Caudal flexion</th>
<th>Rostral flexion</th>
<th>Caudal extension</th>
<th>Rostral extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral</td>
<td>61% (31/51)</td>
<td>2% (1/51)</td>
<td>31% (16/51)</td>
<td>6% (3/51)</td>
</tr>
<tr>
<td>Contralateral</td>
<td>25% (4/16)</td>
<td>0% (0/16)</td>
<td>37.5% (6/16)</td>
<td>37.5% (6/16)</td>
</tr>
</tbody>
</table>

was a CF response evoked by ipsilateral stimulation, while the other two were RE responses evoked by contralateral stimulation.
the full range of behaviors with responses obtained by stimulation in virtually all laminae. Sites where ipsilateral stimulation produced CF responses were interspersed throughout the gray matter, but were most concentrated in laminae III-IV, also the location of cutaneous afferent terminals mediating flexion reflexes (Levinsson et al. 2002). Other than the ipsilateral CF responses concentrated in the deep dorsal horn, no other grouping was apparent. Contralateral stimulation in the dorsal horn produced primarily extensor responses, and a mix of flexor and extensor responses were evoked by stimulation delivered in the white matter.

**EMG analyses**

The criteria described in METHODS excluded the concatenated EMG vectors of 6 of the 67 force fields; the remaining 61 concatenated EMG vectors were analyzed to determine the correlation between active muscles and force pattern type and processed and clustered to determine the influence of position on the relative amplitude of our subset of hindlimb muscle EMGs. For concatenated EMG vectors that divided into at least two clusters, a subsequent cluster analysis was conducted on the normalized individual muscle’s EMGs.

**Correlation analysis results**

Figure 8 presents the relative fraction (expressed in percentage) of the active muscle combinations observed for each force pattern type. Muscles were classified as ankle extensor (AE), ankle flexor (AF), knee extensor (KE), or knee flexor (KF). The frequency at which each of the 16 combinations of muscles was observed for each of the force pattern types suggested a correlation between the muscles used and the force pattern observed. Certain muscle combinations were observed for only one force pattern, but several combinations (e.g., all muscle actives) were observed for more than one force pattern.

Multinomial logistic regression of the correlation between force pattern type (CF, RF, RE, or CE) and muscle (classified as active or not active) showed significance for AE, AF, and KE as parameters in a main effects regression model of force pattern type versus muscles. KF did not show significance, and the predictions of the model were not changed when KF was dropped from the model. Furthermore, the predictive ability was not improved by using a model containing interaction effects. Table 2 summarizes the predictive ability of a model containing AE, AF, and KE as predictors. The overall percentage of correct prediction was 69% (25% predicted by chance), with the prediction ability being lowest for the CE field (17%).

**Cluster analysis of EMG results**

Cluster analysis was used to determine the influence of endpoint position on the hindlimb muscle EMGs (see METHODS). The concatenated EMG vector was clustered with each position forming a case, and the squared Euclidean distance between cases was used as a measure of dissimilarity. The number of clusters was determined by an analysis of the trend in the dissimilarity coefficient as clusters were joined, and a visual analysis of the dendrogram structure. Of the 61 concatenated EMG vectors analyzed (from 61 different stimulation locations), 14 (23%) fell into one cluster using both hierarchi-
cal clustering methods, 28 (46%) fell into one cluster with one of the methods, and 33 (54%) EMG patterns observed during intraspinal microstimulation divided into at least two groups with both methods. The average number of clusters with the average linkage method was 1.7 ± 0.6 and was 1.7 ± 0.5 with Ward’s method. The propensity for an endpoint position to be assigned to a small cluster (i.e., the frequency at which a particular position falls into a minority group) was dependent on the location of the endpoint position. The elements of the smaller cluster(s) were at the edges of the workspace rather than in the center as shown in Fig. 10. These results suggest that muscle activation produced by intraspinal stimulation was modulated by position-dependent sensory feedback and indicate that the modulation occurred mostly at the edges of the workspace.

Of the 33 concatenated EMG vector that divided into a least two clusters with both clustering methods, 32 contained at least one muscle whose normalized EMG divided into at least two clusters across positions with both clustering methods, and the average number of muscles within each concatenated vector that divided into at least two cluster (with both methods) across positions was 2.0 ± 0.9.

An example where the muscle EMGs clustered into a single group is shown in Fig. 9, and limb configuration did not

### Table 2: Force pattern classification by a regression model using activation levels of the ankle extensor, the ankle flexor, and the knee extensor as predictors

<table>
<thead>
<tr>
<th></th>
<th>CE</th>
<th>CF</th>
<th>RE</th>
<th>RF</th>
<th>Percent correct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudal extension (CE)</td>
<td>3</td>
<td>14</td>
<td>1</td>
<td>0</td>
<td>17%</td>
</tr>
<tr>
<td>Caudal flexion (CF)</td>
<td>1</td>
<td>33</td>
<td>0</td>
<td>0</td>
<td>97%</td>
</tr>
<tr>
<td>Rostral extension (RE)</td>
<td>0</td>
<td>2</td>
<td>6</td>
<td>0</td>
<td>75%</td>
</tr>
<tr>
<td>Rostral flexion (RF)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Overall percentage</td>
<td>7%</td>
<td>82%</td>
<td>11%</td>
<td>0%</td>
<td>69%</td>
</tr>
</tbody>
</table>

FIG. 7. Location of stimulation sites within the L5, L6, and L7 segments of the spinal cord at which force fields were measured. Ipsilateral responses are indicated with circles (elongated symbols indicate regions in the dorso-ventral directions in which the response could be elicited), and responses from the contralateral side of the cord are indicated with squares. Colors are used to indicate the type of response.

FIG. 8. Histogram of the frequency of muscle combinations active during intraspinal microstimulation by force pattern type. Muscles are divided as ankle extensor (AE), ankle flexor (AF), knee extensor (KE), and knee flexor (KF). One muscle of each group was recorded during intraspinal microstimulation; muscles were classified as active if they contributed ≥10% of the total EMG (formed by summing the EMGs from all 4 muscles), and inactive if they did not. Number of possible combinations was thus 16 (2⁴), and the relative frequency at which each combination was found for each force pattern was tallied and displayed as a normalized histogram for each force pattern. A number of muscle combinations were uniquely expressed by 1 force pattern, while some combinations were found for more than 1 force patterns.

J Neurophysiol • VOL 91 • JANUARY 2004 • www.jn.org
affect the temporal pattern of any muscle or the relative amplitude of any muscle with respect to the others. An example where the EMGs clustered into two groups is shown in Fig. 9D. The temporal patterns of the EMG of tibialis anterior (TA) and biceps femoris (BF) varied with position, and their normalized EMGs divided into two clusters across positions. In addition, the relative amplitude of the muscles with respect to one another varied across position: vastus lateralis (VL) had its greatest activity in the most extended positions, medial gastrocnemius (MG) had the least activity in the most extended positions, and in the case of BF, the greatest activity was at the intermediate positions and was decreased in both flexed and extended positions. Thus position-dependent modulation of muscle activation was reflected in changes in both the pattern and intensity of muscle activation.

DISCUSSION

The goal of this study was to characterize the endpoint forces elicited by intraspinal microstimulation of the cat lumbar cord. The method involved measuring forces at different endpoint positions and analyzing the EMG patterns to understand how muscle activation varied with position. The data showed that the EMG patterns clustered into groups, indicating that there was position-dependent modulation of muscle activation. This modulation was evident not only in the temporal patterns of muscle activation but also in the relative amplitude of muscle activity.

FIG. 9. A: rectified EMGs of 3 muscles [medial gastrocnemius (MG), vastus lateralis (VL), and tibialis anterior (TA)] for the 9 positions at which forces were measured in 1 animal. Ticks on the abscissa are at 0.2 s. B: binned normalized EMGs for data in A. Binned EMG (10-ms bins) for each muscle at each of the 9 endpoint positions was divided by the sum of the maximum binned EMGs of all the muscles at that endpoint position irrespective of time (the EMG maxima were not taken at 1 time point) to create the normalized bins. These normalized bins ranged from 0 to 1 and described the relative amplitude of each muscle’s EMG with respect to the total EMG signal over time. Ticks on the ordinate are at 0.1, ticks on the abscissa are at 0.2 s. C: EMG vectors formed from data in B. Normalized bins for each muscle were concatenated to create a vector describing total EMG at each position. Each vector formed a case. Cases were clustered to investigate the effects of position on the EMGs. In this example, the vectors formed a single cluster, and we concluded that there was no effect of position on muscular activation measured by the EMG signal. Ticks on the ordinate are at 0.2. D: vectors of concatenated EMG for a different spinal site in the same animal. These vectors divided into 2 clusters, and further analyses indicated that the temporal pattern of TA and BF varied with position.

FIG. 10. Frequency at which endpoint positions fell into the smallest cluster of EMG patterns. Gray circles are for force patterns that were measured over endpoint positions, while black squares are for patterns that were measured over 2 endpoint positions. Marker size indicates the frequency at which the EMG pattern measured at that location fell into the smallest cluster of EMG patterns. Note how the larger markers tend to be at the edges of the workspace.
influence in place. Supraspinal centers tend to be inhibitory, N. These studies were conducted with part of the supraspinal (Gustafsson and Jankowska 1976; McIntyre and Grill 2002).

...direct activation of postsynaptic spinal neurons. Animals (Tresch and Bizzi 1999), further supporting that the... and removal of their influence in place. Supraspinal centers tend to be inhibitory, and removal of their influence by spinal transection should reduce excitation thresholds thus enabling more focal activation. However, acute spinal preparations have elevated stimulation threshold that make it difficult to activate interneuronal elements. A chronic spinal preparation would allow study of the spinal circuitry in isolation, and be more relevant to the clinical study of the use of spinal stimulation for restoration of movement in persons with spinal cord injury.

Although coarse in the volume of neural tissue activated and subject to interpretations as to which neural elements were activated, stimulation unveiled a limited set of endpoint force patterns, as shown previously in the frog and rat. As in the rat, caudal flexion responses were prevalent, but in contrast to the rat, extensor responses were either caudally or rostrally oriented, rather than being strictly caudally oriented (Tresch and Bizzi 1999). Another similarity to the results observed in the rat was the relative paucity of force patterns with equilibrium points. In this study, 4.5% of active fields and 22% of total fields exhibited equilibrium points within the measured workspace, while in the rat, no active field equilibrium point were found. In comparison, 12% of active fields and 70% of total fields exhibited equilibrium points in the measured workspace in frogs (Giszter et al. 1993). Nevertheless, as in the frog, fields measured in cats that converged to equilibrium points were evoked by stimulation in the dorsal and intermediate laminae (regions dominated by interneurons), and never at the deeper sites. Thus although the location of the sites producing force responses with equilibrium points is similar across species, the results in mammals suggest that the relative frequency of fields with equilibrium points is not a universal feature of spinal motor output that is constant across species. Rather, the universal feature seems to be a small number of discrete types of motor responses organized at the level of the spinal cord.

Mechanically, the kinematic arrangement used in this study was different from the one used in the frog and rat, where the hip and knee were free to move and forces were measured at the ankle instead of the paw (foot). This raises the question as to whether the force patterns observed for the two-link limb formed by the lower shank and paw would be similar for the whole limb. Using the Jacobian of each configuration (free vs. fixed femur), one can calculate the joint torques necessary to produce the observed force patterns with either configuration. The knee and ankle torques necessary remain unchanged, while a physiologically feasible hip torque is now required for the three-link limb. Due to the configuration (paw being almost directly under the hip joint), the action of the hip torque on the force vectors is mostly limited to the rostro-caudal plane, and it has little effect on the dorso-ventral orientation of the force vectors. In a limited number of experiments, we have observed that the force patterns obtained with the femur free are similar to the force pattern obtained with the femur fixed. We attribute much of this similarity to the intrinsic biomechanical constraints present in the limb (Bosco et al. 2000). Overall, these arguments seem to indicate that the organization of the force patterns is fairly robust to changes in the number of links, although additional data are required to confirm these results.

Compared with other data on the endpoint behaviors obtained during microstimulation of the lumbar spinal cord of cats, our results exhibit a greater variety of endpoint force responses for stimulation in the dorsal (laminae I–V) and intermediate (laminae VI–VII) locations. In awake or pentobarbital anesthetized spinal intact cats with chronically implanted electrodes, only flexion movements were obtained from the dorsal and intermediate regions of the spinal cord, while extensor responses were obtained only from stimulation in the ventral motor nuclei (Mushahwar et al. 2002). In a previous study with acutely implanted electrodes and conducted on anesthetized, decerebrate, and acutely spinalized animals, movements of the endpoint in all directions could be obtained by stimulation delivered into the intermediate regions of the cord (Stein et al. 2002). However, the stimulation levels

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**Force response produced by intraspinal stimulation**

Electrical stimulation is a nonphysiological means to activate groups of neurons. The results, however, are consistent with behaviors evoked by more natural stimulation (e.g., flexion withdrawal reflexes) and may reflect functional organization within the spinal cord (Graziano et al. 2002). The volume of neural tissue activated by our stimulation paradigm is estimated to have a radius of 250–500 μm (Gustafsson and Jankowska 1976; Porter 1963). A variety of neural elements may be activated within that volume including cells, axons, and dendrites, but prior results suggest that the responses evoked by intraspinal microstimulation are the result of direct activation of postsynaptic spinal neurons. The threshold for activation of presynaptic terminals projecting into the region of stimulation is often less than or comparable to the threshold for direct excitation of local cells (Baldassera et al. 1972; Gustafsson and Jankowska 1976; Jankowska et al. 1975; McIntyre and Grill 2002). Thus indirect effects mediated by synaptic transmission may alter the direct effects of stimulation on the postsynaptic cell. However, during extracellular stimulation action potential initiation occurs in the axon at some distance from the integration of synaptic inputs in the soma (Nowak and Bullier 1998a,b). The effects of co-activation of presynaptic fibers on firing in the postsynaptic cell are therefore minimal (Gustafsson and Jankowska 1976; McIntyre and Grill 2002). Furthermore, the flexion responses evoked by intraspinal stimulation in deafferented animals were similar to those in intact animals (Tresch and Bizzi 1999). Another similarity to the results observed in the rat was the relative paucity of force patterns with equilibrium points. In this study, 4.5% of active fields and 22% of total fields exhibited equilibrium points within the measured workspace, while in the rat, no active field equilibrium point were found. In comparison, 12% of active fields and 70% of total fields exhibited equilibrium points in the measured workspace in frogs (Giszter et al. 1993). Nevertheless, as in the frog, fields measured in cats that converged to equilibrium points were evoked by stimulation in the dorsal and intermediate laminae (regions dominated by interneurons), and never at the deeper sites. Thus although the location of the sites producing force responses with equilibrium points is similar across species, the results in mammals suggest that the relative frequency of fields with equilibrium points is not a universal feature of spinal motor output that is constant across species. Rather, the universal feature seems to be a small number of discrete types of motor responses organized at the level of the spinal cord.

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**Bar spinal cord.** As observed in other species, we found that the hindlimb endpoint forces could be grouped into a small number of directionally arranged patterns, suggesting a modular organization to the spinal cord motor output. These force patterns were produced by coactivation of the hindlimb’s muscles, with affenter feedback acting to modulate the activation of the muscles. Some of the force patterns, and the localization of the sites producing them, are consistent with the notion that electrical stimulation activates some of the neural circuitry of established reflexes.

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**J Neurophysiol • VOL 91 • JANUARY 2004 • www.jn.org**
used (2–300 μA current pulse for the chronic experiments, 
\( \leq 500 \) μA in the acutely spinalized preparation) were higher
than the levels in the present study and sufficient to activate
volumes of tissue with diameters \( \leq 3,000 \) μm (Porter 1963).
Although responses with lower thresholds of activation may
have been masked when larger volumes of neural tissue were
activated, these results also suggested that a limited number of
movement types were produced by intraspinal microstimula-
tion. It is difficult to compare these results to data from studies
that recorded responses at single joints since it is not possible
to infer the torque(s) at the other joint(s).

Relationship to functional reflexes and the neurons
mediating them

Some of the force patterns evoked by intraspinal stimulation
are reminiscent of the functional reflexes described by Sher-
lington. The caudal flexion response is extremely similar to the
classic flexion reflex, while the caudal extensor fits Sher-
lington’s description of the “extensor thrust.” Stimulating con-
tralateral to the recorded limb produced a number of extensor
responses (caudal and rostral) that were likely related to the
crossed extension reflex (coincident flexion of the contralateral
limb was not observed due to its surgical denervation). Al-
though Sherrington described the crossed extension reflex as
strictly a caudal extensor, we also observed extensor responses
that were rostrally oriented. While two of the force patterns
found have thus been described in relation to known reflexes,
the rostral extensor is not mentioned in the reflex literature.
Furthermore, rostral flexion may be part of a scratch reflex,
although this particular force pattern was rarely observed and
may have been an anomaly.

The locations of the first order interneurons (and some of the
last order interneurons) mediating spinal reflexes have been
studied extensively in the cat (reviewed in Jankowska 1992;
McCrea 1986), and the locations of stimulation can be related
to some of the topology of the interneuronal circuitry. A large
number of the ipsilateral flexion responses and contralateral
extension responses occurred in response to stimulation in
known regions of termination of cutaneous afferents (laminae
II–IV) (Levinsson et al. 2002). Stimulation in this area may be
activating the incoming afferents or first order inter/projection-
neuron populations, as the thresholds for pre- and postsynaptic
elements are similar (Baldissera et al. 1972; Gustafsson and
Jankowska 1976; Jankowska et al. 1975; McIntyre and Grill
2002). Interestingly, flexion responses could still be evoked in
daafferented animals when stimulating in the dorsal regions of
the cord (Tresch and Bizzi 1999), suggesting that it is the
postsynaptic elements that are responsible for the observed
responses. A mix of extension and flexion responses were
evoked by stimulation in lamina VII, which contains a number
of first order inhibitory interneurons that mediate reciprocal
inhibition of motoneurons and are activated by the Ia and Ib
afferents. Dendrites from motor neurons also extend into this
region, and a number of responses seen for stimulation at these
depths resemble responses obtained during direct activation of
the motoneurons (i.e., short latency, constant force and EMG
with durations that matched the duration of the stimulus train).
A number of the responses though had variations during the
activation period that were not consistent with direct motoneu-
ronal activation and may have been mediated by interneuronal
connections.

The force responses described in this report are consistent
with a number of spinal reflexes and consistent with a modular
organization of the spinal motor output. The circuitry involved
and its relationship to the body of literature on spinal interneu-
rons, however, are not clear. It is possible that the apparent lack
of mapping may be due to the grouping of all responses at one
level of the segment. Normalization of the segment to account
for differences in size between animals (see Vanderhorst and
Holstege 1997) would have allowed us to pool the data of all
the animals by localizing each response within a finer rostro-
caudal segment. In the future, following such normalization
procedure may reveal a rostro-caudal organization to the re-
ponses. Furthermore, our sampling of spinal sites was also
biased and nonuniform as we purposefully looked for regions
producing robust stable responses rather than systematically
investigate the rostro-caudal and medio-lateral spinal organi-
zation by selecting our penetration sites on a grid pattern. We
have previously generated fine grained maps of the isometric
knee torque evoked by intraspinal microstimulation, and these
maps revealed consistent dorsal regions that evoked ipsilateral
flexion and contralateral extension (Giszter et al. 2001). The
time required to investigate with fine spatial sampling the
endpoint force responses at nine limb configurations would far
exceed the usable experimental time with an animal. Further-
more, the crudeness of the regions activated with electrical
stimulation, the number of different neural elements in close
proximity, and the apparent intermingling of different types of
inter- and projection-neurons makes it difficult to determine the
populations of neurons that contributed to the observed re-
ponses.

Spinal mechanism of control—implications of the EMG data

Clustering methods were used to determine if the patterns of
normalized EMGs varied with the position of the endpoint. The
results supported the hypothesis that the activation level of at
least some of the monitored muscles varied with position, and
that the observed force patterns were the result of sensory
feedback in addition to the intrinsic biomechanical properties
of the musculoskeletal system. A number of EMG patterns (54% of EMG patterns observed
during intraspinal microstimulation divided into at least 2
groups) showed variations in the relative magnitudes of the
EMGs at different endpoint positions. This indicated that mus-
cle activation was modulated via position-dependent sensory
feedback. These effects were most pronounced at the borders
of the sampled workspace where the activation of sensory
inputs is expected to be the most robust. This result suggests
that the force patterns evoked by intraspinal stimulation are not
fixed input–output relationships, but rather, the response
evoked by stimulation can be modulated by sensory input to
the spinal circuitry.

A possible alternative interpretation is that the changes in
EMG with limb configuration were the result of position-
dependent pick up by the intramuscular EMG electrodes. How-
ever, several arguments suggest that this is not the case. First,
a number of the EMG patterns measured (28 of 61) did not
show changes in magnitude with changes in limb configuration
even though the relative changes in electrode positions were
comparable. This was true both within and across animals. Second, while a significant proportion the EMG patterns fell into a single cluster (23–46%), a number (3 of the 5 EMG patterns with significant EMGs in all 4 muscles) showed modulation on all four electrodes. This simultaneous modulation of activity on all electrodes is unlikely to be due strictly to position-dependent variations in the electrode pick-up, and crosstalk of EMG activity between these muscle groups is limited with bipolar intramuscular recording electrodes. The results thus suggest that afferent feedback modifies the muscular activity produced by intraspinal microstimulation, especially at the edges of the workspace. This finding is not consistent with the results of Loeb et al. (1993), who concluded that muscular activation by intraspinal microstimulation of the frog spinal cord is a feed-forward mechanism based on 1) the absence of changes in the active muscles or the rank ordering of their average EMG magnitudes during intraspinal microstimulation before and after deafferentation, and 2) the absence of changes in the rank ordering of the average EMG magnitudes with changes in limb position. Even though our data analysis was not based on strictly comparing magnitudes, we frequently observed changes in the rank ordering of the average EMG magnitudes in our data. Differences between these two studies may be due to the fact that the fields studied by Loeb et al. were dominated by hip flexion and did not include substantial activity in the ankle musculature or the hip extensors. Thus their results may reflect an ordering in the recruitment of the hip flexors only. Furthermore, their experiments were conducted in spinal frogs, and the apparent difference in position-dependent modulation of muscle activation may reflect different in the relative strengths of sensory feedback between the two preparations.

Implications for artificial control of motor function

The results of this study indicate that intraspinal microstimulation generates organized multiple joint motor responses that engage activity in multiple muscles. The characteristics of these responses differed from those obtained by direct muscle activation—either via intramuscular stimulation or by intraspinal stimulation in the deep ventral horn. These results support the concept that electrical activation of spinal neural circuits by intraspinal stimulation may simplify the artificial control of multi-joint motor function (Barbeau et al. 1999; Grill 2000).

Generation of complex behaviors such as reaching or locomotion requires large numbers of muscles to be activated. With electrodes placed in the periphery, this requires that at least one electrode be placed in or on each muscle or muscle nerve (Grill 2001). Similarly, if motor neurons were activated in the ventral horn, it seems likely, based on the anatomy of the spinal motor neurons pools (Burke et al. 1977; Vanderhorst and Holstege 1997), that several microelectrodes would be required to achieve complete activation of a single muscle (Mushahwar and Horch 1997). Therefore control of many muscles by stimulation of motor neurons will require many electrodes. In contrast, interneurons have divergent projections (Jankowska 1992), and activation of small groups of interneurons is expected to lead to activation of larger groups of motor neurons (e.g., McCrea et al. 1995).

The present results and those of previous studies reveal that the motor responses produced by intraspinal stimulation are of a few limited types (Giszter et al. 1993; Lemay et al. 2001; Tresch and Bizzi 1999). The magnitude of endpoint forces can be controlled by modulation of stimulus amplitude (Lemay et al. 2001), and perhaps most importantly, the endpoint force vectors (“force field”) produced by one microelectrode adds vectorially to the endpoint force vectors produced by a second microelectrode, and the contribution of each can be scaled by the stimulus intensity (Lemay et al. 2001; Mussa-Ivaldi et al. 1994). Thus summation of motor responses evoked by intraspinal stimulation has been demonstrated and provides a mechanism by which few electrodes, producing a few unique patterns of endpoint forces, can be used to synthesize complex behaviors.

GRANTS

This work was supported by National Institute of Neurological Disorders and Stroke Grant NS-8-2300.

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