Decorrelating Actions of Renshaw Interneurons on the Firing of Spinal Motoneurons Within a Motor Nucleus: A Simulation Study

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Maltenfort, Mitchell G., C. J. Heckman, and W. Zev Rymer. Decorrelating actions of Renshaw interneurons on the firing of spinal motoneurons within a motor nucleus: a simulation study. *J. Neurophysiol.* 80: 309–323, 1998. A simulation of spinal motoneurons and Renshaw cell was constructed to examine possible functions of recurrent inhibition. Recurrent inhibitory feedback via Renshaw cells is known to be weak. In our model, consistent with this, motoneuron firing was only reduced by a few pulses per second. Our initial hypothesis was that Renshaw cells would suppress synchronous firings of motoneurons caused by shared, dynamic inputs. Each motoneuron received an identical pattern of noise in its input. Synchrony coefficients were defined as the average motoneuron population firing relative to the activity of selected reference motoneurons; positive coefficients resulted if the motoneuron population was particularly active at the same time as the reference motoneuron was active. With or without recurrent inhibition, the motoneuron pools tended to show little if any synchronization. Recurrent inhibition was expected to reduce the synchrony even further. Instead, it reduced the variance of the synchrony coefficients, without a comparable effect on the average. This suggests—surprisingly—that both positive and negative correlations between motoneurons are suppressed by recurrent inhibition. In short, recurrent inhibition may operate as a negative feedback mechanism to decorrelate motoneurons linked by common inputs. A consequence of this decorrelation is the suppression of spectral activity that apparently arises from correlated motoneuron firings due to common excitatory drive. Without recurrent inhibition, the power spectrum of the total motoneuron pool firings showed a peak at a frequency corresponding to the largest measured firing rates of motoneurons in the pool. Recurrent inhibition either reduced or abolished this peak, presumably by minimizing the likelihood of correlated firing among pool elements. Renshaw cells may act to diminish physiological tremor, by removing oscillatory components from aggregate motoneuron activity. Recurrent inhibition also improved coherence between the aggregate motoneuron output and the common drive, at frequencies above the frequency of the ‘‘synchronous’’ peak. Sensitivity analyses demonstrated that the spectral effect became stronger as the duration of inhibitory synaptic conductance was shortened with either the magnitude or the spatial extent of the inhibitory conductances increased to maintain constant net inhibition. Overall, Renshaw inhibition appears to be a powerful way to adjust the dynamic behavior of a neuron population with minimal impact on its static gain.

INTRODUCTION

The Renshaw cell is one of the few spinal interneurons that has been investigated intensively. Its location, firing behavior, and connections to other neurons and firing behavior are all well established (for review see Windhorst 1990). Despite this, its functional role in the nervous system remains a matter for debate.

The inhibition of motoneurons by the Renshaw cells they drive suggests a simple negative feedback system. Such feedback should regulate motoneuron activity in some useful way. One theory proposed was that Renshaw cells could suppress motoneuron response to weak inputs (Brooks and Wilson 1959; Granit and Renkin 1961). Another theory was that Renshaw cells may adjust the gain of the motoneuron pool (Hultborn et al. 1979a).

Weighing against such hypotheses is physiological evidence that Renshaw cell inhibition may be too small to produce the necessary modulation of motoneuron firing (Eccles et al. 1961; Hultborn et al. 1988b; Lindsay and Binder 1991). Furthermore, pharmacological blockade of Renshaw cell firing does not produce an increase of motoneuron activity (Redman and Lampard 1967; Windhorst et al. 1978).

Although recurrent inhibition does not seem to affect total motoneuron activity, it may be able to affect the relative timing of motoneuron firings. The recurrent inhibitory postsynaptic potential (IPSP) produced by synchronous Renshaw volleys is of the same order of magnitude as the afterhyperpolarization of motoneurons (Hultborn et al. 1979b) and so should have similar impact on the interspike interval of active motoneurons. Previous reports have shown that Renshaw cell firing can affect motoneuron firing synchrony (Adam et al. 1978; Windhorst et al. 1978). Motoneuron firing synchrony in turn can be linked to tremor (Allum et al. 1978; Dietz et al. 1976).

Synchronous motoneuron firings should result when the motoneurons are excited by a shared, dynamic synaptic input, which may come from either segmental or supraspinal sources. Our hypothesis was that recurrent inhibition should reduce synchrony between motoneurons receiving such a synchronizing input. In an experimental preparation, it is not practical to examine synchrony beyond the level of pairs of motor units. It is also difficult to pharmacologically block inhibition from, or excitation to, Renshaw cells without affecting other inputs to the motoneuron pool. Therefore, to explore the potential actions of Renshaw cells on a motoneuron pool, we developed a computer model of a motor nucleus with recurrent inhibition.

The recurrent inhibitory circuit is particularly well suited for study by computer simulation. The membrane properties and firing behavior of motoneurons are well described in the literature (Gustaffson and Pinter 1984; Heckman and Binder 1991). Although membrane properties of Renshaw cells are
not as well known, there is enough information about their firing behavior and effects on motoneurons to build an acceptable functional model.

Previous efforts (e.g., Koehler and Windhorst 1985; Stein and Oguztöreli 1984) to model this circuit have used smooth functions describing mean firing rates to represent the motoneuron and Renshaw cell populations. This approach does not allow for observation of synchronous firing between motoneurons, although Koehler and Windhorst (1985) could describe phase shifts between linear functions representing subpopulations of motoneurons.

The model of recurrent inhibition presented in this study is the first to use broadly realistic spiking neuron models and synaptic conductances. A previous effort (Akazawa and Kato 1990) used spiking neurons, but synaptic effects were mediated by voltage waveforms based on recorded postsynaptic potentials and not by active conductances. This may be a significant limitation, as the recurrent inhibitory current on motoneurons close to firing threshold may be twice that on motoneurons at rest (Lindsay and Binder 1991). The IPSP produced by a Renshaw cell may depend on both the driving potential on the motoneuron and the motoneuron’s recent firing history; that is, whether the target motoneuron was depolarized or hyperpolarized at the time the Renshaw cell fires.

In this study, we found that the relatively weak recurrent inhibition was capable of reducing the frequency and magnitude of correlations between motoneurons. However, our hypothesis predicted that only positive correlations—indicating simultaneous firings of motoneurons—would be affected. Contrary to our expectations, recurrent inhibition suppressed both positive and negative correlations, each to a comparable degree. This means that recurrent inhibition may operate as a negative feedback mechanism to decorrelate motoneuronal firing rather than merely desynchronizing motoneurons. A direct result of this mechanism is the suppression of spectral activity that apparently arises from phase-locked motoneuronal firing.

Methods

Overview of the model

At the outset, it is important to acknowledge that this is not a perfectly realistic model of motoneurons or of recurrent inhibition. Instead the goal of this work was to produce an observable system the individual components of which reproduce observed behaviors of their physiological counterparts. The behaviors include those relevant to the steady-state firing of a motoneuron pool receiving a synchronizing drive. With this system, it was possible to set the drive to the motoneuron pool and the strength of recurrent inhibition and to observe the behavior of any or all of the simulated motoneurons.

Parameters for simulated motoneurons were based on published values for passive electrical properties, afterhyperpolarization size, and duration, and the relation between firing rate and input current (Gustaffson and Pinter 1984; Heckman and Binder 1991; Hultborn et al. 1988a; Kernell 1979; Zengel et al. 1985). The simulated Renshaw cells were homogeneous, as no data were available on variability of Renshaw cells within a pool. The Renshaw cell parameters were assigned to reproduce behavior observed by Hultborn and Pierrot-Deseilligny (1979). Similarly, the magnitude, time course, and spatial range of synapses between motoneurons and Renshaw cells were set to match electrophysiological data (Hamm et al. 1987b; Hultborn et al. 1988b; Lindsay and Binder 1991; van Kuenlen 1981) and anatomic studies (Cullheim and Kellerth 1978; Lagerbäck and Kellerth 1985a).

Our simulations were based on 256 motoneurons, which is close to the number of cells in the cat medial gastrocnemius pool (~270) (Burke 1981). The motoneurons were arranged along a 4 × 64 grid (mediolateral by rostrocaudal). A single column of 64 Renshaw cells was arranged along the rostrocaudal axis of the motoneuron grid, so each Renshaw cell would interact with four motoneurons at the same rostrocaudal level. There are no published figures for the size of the Renshaw cell population involved with a given motor nucleus, so the decision to have 64 Renshaw cells was for mathematical convenience. The motoneurons were distributed along a tenfold continuum of rheobases (see the following text).

Members of each neuron population were represented by a point neuron model (MacGregor 1987; MacGregor and Oliver 1974), defined as a “leaky integrator” with an exponentially decaying potassium conductance representing the afterhyperpolarization. The model neuron fires when the sum of its excitatory and inhibitory inputs crosses a voltage threshold, at which time synapses on target cells are fired and the afterhyperpolarization conductance is increased. The model was modified to explicitly include an input resistance parameter to model motoneurons of varying rheobases. While relatively simple, this model captured the firing behavior of neurons efficiently. With linear summation of afterhyperpolarization conductances, the MacGregor neuron model demonstrates a linear rate/current relationship in the steady-state (MacGregor and Oliver 1974).

Parameterization of motoneurons

For each trial, each of the 256 motoneurons was assigned randomly a current threshold for steady firing using an exponential distribution

\[
\text{thi} = 4.0 \exp\left[\ln(10.0)i + r_i\right]
\]  \hspace{1cm} (1)

where \( \text{thi} \) was the current threshold of unit \( i \) and \( r_i \) was a random variable uniformly distributed between 0 and 1. This produced an exponential distribution of current thresholds in the range 4–40 nA. Half of the simulated motoneuron population have current thresholds of 4–14 nA, whereas the other half (the “large” cells) have thresholds ranging from 12 to 40 nA.

Other parameters were generated from the current threshold, producing values in general agreement with the data presented by Gustaffson and Pinter (1984).

Voltage threshold varied linearly with current threshold

\[
V_i = 5 + (\text{thi} + 20)/12 \quad \text{(range 10–25 mV)}
\]  \hspace{1cm} (2)

Input resistance was the voltage threshold divided by the current threshold

\[
R_i = V_i/\text{thi} \quad \text{(range 0.625–2.5 M\Omega)}
\]  \hspace{1cm} (3)

Motoneuronal time constants were proportional to resistance

\[
\tau_i = 4 + R_i \quad \text{(range 2.5–10.0 ms)}
\]  \hspace{1cm} (4)

Gustaffson and Pinter (1984) noted that the systematic differences in voltage threshold might reflect cell-impalement injuries. The possible impact of these differences on the simulation results is considered in the sensitivity analysis at the end of the RESULTS. Similarly, membrane time constant is not strictly dependent on input resistance of the motoneuron within unit types (Zengel et al. 1985). There is evidence that a linear relationship between the two parameters exist along the continuum of resistance values (Gustaffson and Pinter 1984; Zengel et al. 1985). A linear relation-
ship was assumed in this model for simplicity. The time constant controls the rate of change of the neuron membrane potential $E_i$ in response to its inputs

$$\frac{dE_i}{dt} = -E_i + R_i[I - \Sigma G_{syn}(E_i - E_{syn}) + G_{syn}(E_i - E_0)]/\tau_i$$  \hspace{1cm} (5)$$

where $R_i$ and $\tau_i$ are as defined in Eqs. 3 and 4; the magnitude of afterhyperpolarization conductance $G_{syn}$, depends on the afterhyperpolarization parameters $B_i$ and $T_{E Ki}$ described later; $E_0$ is the equilibrium potential of the potassium conductance (defined as 10 mV below resting potential); the terms $G_{syn}$ and $E_{syn}$ in the summation describe the conductance and equilibrium potentials of synapses exciting or inhibiting the neuron; and $I$ is the current that is used to activate motoneurons (see further text).

The afterhyperpolarization was described by two parameters, peak conductance $B_i$ and time constant $T_{E Ki}$, representing the size and decay time constant of the potassium conductance opened with each cell firing. With each neuronal firing, its afterhyperpolarization conductance $G_{syn}$, was incremented by $B_i$. The rate/current slope of a modeled neuron depends nonlinearly on the size and duration of its afterhyperpolarization and on its voltage threshold (MacGregor and Oliver 1974).

The $B_i$ and $T_{E Ki}$ parameters of the afterhyperpolarizations were adjusted to meet three constraints: the afterhyperpolarization amplitude and duration varied inversely with current threshold (Gustafsson and Pinter 1991); the minimum steady firing rate linearly increased with current threshold, from 8 to 20 Hz (Heckman and Binder 1991; Kernell 1979); the slope of the firing rate/current relation for all motoneurons was $\sim 1.5$ pps/nA (Kernell 1979; Schwinding 1973). For several motoneurons along the range of current thresholds, afterhyperpolarization parameters were determined empirically that meet these three criteria. Polynomial fits were used to interpolate $B_i$ and $T_{E Ki}$, as functions of rheobase, and several interpolated values were examined to confirm good behavior. From the smallest to the largest motoneuron, the values of $T_{E Ki}$ varied from 64.6 to 18.24 ms, whereas the values of $B_i$ varied from 0.5 to 1.0 μS.

Powers and Binder (1996) found that a motoneuron model required a substantial increase in input conductance during repetitive firing to produce a realistic firing response to transient inputs. In our model, an increased input conductance was provided by theafterhyperpolarization. The peak afterhyperpolarization conductance after a single motoneuron firing ranged from 62% (on the smallest-resistance motoneurons) to 126% (on the largest-resistance motoneurons) of the resting conductance. Similar relative magnitudes, though no size dependencies, were reported by Schwinding and Calvins (1973). The absolute magnitudes of peak afterhyperpolarization conductance ($B_i$; see preceding text) increased twofold from largest- to smallest-resistance motoneurons.

Parameterization of Renshaw cells

No direct measurements of Renshaw cell membrane properties were available at the time of this work. Renshaw cells are smaller than the smallest type S motoneuron and have fewer dendrites (Lagerbäck and Kellerth 1985a,b), so it was assumed they would have a higher input resistance. Accordingly, 4 MΩ was used. The 30-ms afterhyperpolarization of Renshaw cells reported by Hultborn and Pierrot-Deseilligny (1979) indicates that the time constant of the Renshaw cell was $\sim 8$ ms. Afterhyperpolarizations of 30-ms duration and both transient and steady-state rate/current slopes agreeing with the observations of Hultborn and Pierrot-Deseilligny (1979) were produced by empirically determining appropriate values of $B_i$ and $T_{E Ki}$ for the Renshaw cell, as described previously for motoneurons.

Spontaneous background firing of Renshaw cells was generated by assigning the simulated Renshaw cell a negative firing threshold. There was no quantitative data concerning descending inputs to the Renshaw cell at the time of this work, although observed spontaneous firing of Renshaw cells may be due to activation of muscarinic acetylcholine receptors (Curtis and Ryall 1966a–c) via descending excitatory pathways (Haase and van der Meulen 1961; Kaneko et al. 1987; Morales et al. 1988). Other synaptic and neuromodulatory inputs to Renshaw cells are reviewed by Baldissera et al. (1981), including the possibility of excitation from tonically firing gamma motoneurons.

Connectivity of pool

MAGNITUDE AND DURATION OF SYNAPSES. Each synapse was modeled as a conductance decaying exponentially from an instantaneous rise. Synaptic conductances arriving at different times or from different sources were assumed to sum linearly. The shape of the resulting postsynaptic potential depended on the membrane potential, time constant, and resistance of the target neuron, which might be modified by temporal and spatial summation of the synaptic conductances and by the afterhyperpolarization conductance.

The average magnitude of motoneuron synapses on Renshaw cells was scaled with motoneuron current threshold (Cullheim and Kellerth 1978; Hultborn et al. 1988b). On the basis of the distribution of motoneuron axonal collateral swellings with axon diameter (Cullheim and Kellerth 1978), the function used to match Renshaw cell excitation to motoneuron size was

$$G_i = \frac{G_{syn}(1/0.8 + \text{thr}_r - 4.0)/36.0}{(6)}$$

where $G_i$ was the average excitatory conductance to an Renshaw cell from motoneuron with current threshold $\text{thr}_r$, as described above (Eq. 1); and $G_{syn}$ was the size of the excitatory conductance a Renshaw cell receives from the firing of the smallest (threshold 4 mA) motoneuron ($G_i = 7–35$ nS). This approximation was selected to match the quantitative proportions of axon collaterals belonging to motoneurons associated with slow-twitch (S), fast, fatigue-resistant (FR), and fast, fatiguable (FF) motor units.

An excitatory postsynaptic potential (EPSP) on Renshaw cells can last 50–60 ms (Walmsley and Tracey 1981). The long duration was attributed to synaptic barriers against the reuptake of acetylcholine, the neurotransmitter that excites Renshaw cells (Curtis and Eccles 1958). A 15-ms time constant was used for the decay of the excitatory conductance. The resulting EPSP on simulated Renshaw cells decayed to 10% of its peak value after the activation of the excitatory synapse.

We assumed that the input from motoneurons would not saturate the firing rates of Renshaw cells. Such saturation has been seen in studies of Renshaw cells activated by ventral root stimulation (Christiaatos et al. 1987; Cleveland et al. 1981), but other studies contradict this (Hultborn et al. 1979b; Ross et al. 1972, 1982). Orthodromic activation of Renshaw cells is less efficient in activating Renshaw cells (Hultborn et al. 1988b; Ryall et al. 1972), indicating that naturally activated Renshaw cells would not be stimulated at the rates at which saturation occurred. Therefore, excitation from motoneurons was set so that Renshaw cells would fire below the 200 pps maximum observed by Cleveland et al. (1981). It should be noted that Cleveland et al. (1981) attributed the saturation to shunting from the opening of excitatory synapses on the Renshaw cell membrane and that the same shunting is possible in the neuron model used in this study.

The IPSP from Renshaw cells onto motoneurons was parameterized by a peak synaptic conductance of 36 nS, an equilibrium potential of $-7.5$ mV (relative to resting potential) and a decay time constant of 5 ms. The resulting average IPSP (across all motoneurons) resembled that reported by van Kuilen (1981).

Synaptic connection patterns

Synapses arising from both Renshaw cells and motoneurons decayed symmetrically along the rostrocaudal dimension of the model.
grid. Along the mediolateral/dorsoventral dimension of the grid, where one Renshaw cell can synapse on four motoneurons, synapses were constant and extended over the entire row. This distribution of axonal connections assumes that decay with distance is only along the rostrocaudal dimension of the grid. This is reasonable given that motor nuclei in the cat are arrayed as rostrocaudally oriented columns (Romanes 1951).

The magnitude of each synaptic conductance impacting on a target neuron was multiplied by the value of \( W \) corresponding to the rostrocaudal distance between the firing neuron and its target, where \( W \) was defined by

\[
W = K/(1 + 16(d/d_{\text{max}})^2)
\]  

(7)

where \( W \) was the weighting, \( d \) was the rostrocaudal distance between a firing neuron and its target, and \( d_{\text{max}} \) was the maximum distance for that neuron’s axonal connections, both measured in rows of simulated neurons. \( K \) was selected so that the average value of \( W \) along the rostrocaudal distribution was 1.0. Each axon could reach target neurons along a total of \( 2 * d_{\text{max}} + 1 \) rows, centered at the row occupied by the presynaptic neuron.

This distribution produced a Gaussian central peak with long tails, which agreed with the observed distribution of Renshaw cell synapses (Hamn et al. 1987b; Lagerbück and Kellerth 1985a; Windhorst and Kokkoroyiannis 1991). Histograms of the distribution of motoneuron axon collaterals (Cullheim and Kellerth 1978) indicated that this choice for motoneuron to Renshaw cell synapses was not inappropriate.

In this study, \( d_{\text{max}} = 15 \) for the inhibitory synapses from Renshaw cells to motoneurons and \( d_{\text{max}} = 2 \) for the excitatory synapses from motoneurons to Renshaw cells. These values were estimated from published physiological measurements, as described next.

The maximum effective synaptic current on resting motoneurons due to steady-state Renshaw cell firing was \( -0.42 \) nA (Lindsay and Binder 1991), but that inhibition was produced by maximal stimulation of the heteronymous nerve. The difference in corresponding recurrent IPSPs can be twofold between the heteronymous and the homonymous case ( Eccles et al. 1961) so we set the magnitude in the simulation to be \( -0.84 \) nA. The maximum steady-state firing rate of Renshaw cells is \( \sim 200 \) pps ( Cleveland et al. 1981), and we estimated the number of Renshaw cell synapses on motoneurons using the synaptic parameters

\[
(\text{synaptic current})/(\text{max firing})*\text{synaptic time constant}
\]

\[
= -0.84 \text{nA}/(200 \text{ppps} / 7.5 \text{mV} / 36 \text{nA}) = 31.111
\]

In the model, each Renshaw cell had a range of \( \pm 15 \) rows rostrocaudal (\( d_{\text{max}} = 15 \) in Eq. 7), so that each motoneuron would receive inhibitory input from 31 Renshaw cells. Assuming that the MG pool is \( 6-8 \) mm long rostrocaudally, this corresponds to a spatial range of \( \pm 1.6 \) mm as reported by Hamn et al. (1987b).

The variations in IPSP from Renshaw cells due to rostrocaudal weighting and motoneuron properties created a 34-fold range of PSP amplitudes with the same maximum, minimum, and mean (55, 1.6, and 12.5 \( \mu \text{V} \)) reported by van Kuenlen (1981).

Published literature indicates that a single firing of a motoneuron gives rise to a compound recurrent IPSP that is four to six times the size of mean unitary IPSPs from Renshaw cells (Hamn et al. 1987a; van Kuenlen 1981). Each simulated motoneuron therefore synapsed on five Renshaw cells (\( d_{\text{max}} = 2 \)). Making this estimate is tricky, given that there are four to six spikes in a Renshaw cell burst ( Eccles et al. 1954; van Kuenlen 1981), and resulting recurrent IPSPs may not sum linearly. Measurements of population IPSPs ( Eccles et al. 1954; Friedman et al. 1981; Lindsay and Binder 1991) cannot be compared with the Hamn studies because each Renshaw cell may be activated by more than one motoneuron.

Because of the columnar organization of the simulation, with 4 motoneurons along a row, each Renshaw cell could receive input from 20 motoneurons.

SIMPLIFYING ASSUMPTIONS. Certain features that may be present in the biological circuit were neglected deliberately in this study to make the simulation tractable within the limits of physiological observations (or lack thereof) and computing resources. The following are assumptions made beyond those previously stated or target neuron was multiplied by the value of \( W \) corresponding to the rostrocaudal distance between the firing neuron and its target, where \( W \) was defined by

Because of the columnar organization of the simulation, with 4 motoneurons along a row, each Renshaw cell could receive input from 20 motoneurons.

There are no Renshaw cell-Renshaw cell synapses. There are no motoneuron-motoneuron synapses. The only currents present in the neuron model, besides the stochastic input to the motoneurons, were the excitatory input to Renshaw cells from motoneurons, the inhibitory input to motoneurons from Renshaw cells, and the afterhyperpolarization conductances present in both neuron types. For computational speed, and because not all the information necessary for accurate modeling was available, no other currents were considered. One consequence of this was that the voltage thresholds of the simulated motoneurons were fixed. There was no postinhibitory rebound of motoneurons, although the magnitude of Renshaw cell inhibition is small enough for this effect to be negligible.

Another, perhaps more important issue is that plateau potentials that may allow motoneurons to tonically fire in the absence of external inputs (cf. Hounsgaard et al. 1988) also were excluded. Granit et al. (1960) showed that increased inhibition from Renshaw cells could stop tonically firing motoneurons in a manner consistent with the disruption of plateau potentials. Although the inhibition was increased using ventral root shocks, which may be stronger than normal physiological activation, this role cannot be ruled out.

A much more detailed motoneuron model would be required to generate plateau potentials, and we considered this beyond the scope of the present work.

There are no motoneuron-motoneuron synapses. There is some indication that motoneurons synapse on each other via axon collaterals (Cullheim and Kellerth 1978). This is only a small fraction of the bulk of axonal swellings and may be on Renshaw cell dendrites that happen to travel into the motor nucleus region. In this simulation, excitatory linkages between motoneurons were considered to be absent.

There are no Renshaw-cell-Renshaw cell synapses. Evidence indicates that Renshaw cells may inhibit each other (Renshaw 1946; Ryall 1970, 1981; Ryall et al. 1971), but the existence of mutual inhibition between Renshaw cells activated by motoneurons belonging to the same pool is debated. It had been suggested that the pause after the Renshaw cell burst produced by a ventral root shock was the result of inhibition from other Renshaw cells excited by the same stimulus (Ryall et al. 1971). Yet this pause is not affected by glycine antagonists ( Curtis et al. 1976) and has too short a latency to be postsynaptic (Kokkoroyiannis et al. 1989).

In this study, it was assumed that inhibition between Renshaw cells innervated by the same motor pool is negligible. Possible effects of inhibition between two populations of Renshaw cells, each innervated by a separate (not necessarily antagonistic) (cf. Ryall 1981) motor pool, are considered in Sensitivity analysis.

Synapses are homogeneous. The simulation assumes that only two types of synapses exist, excitatory from motoneurons onto Renshaw cells, and inhibitory from Renshaw cell to motoneurons. Both types of synapses have been found to be further subdivided, although in neither case was there enough information to adequately represent these subdivisions in the model.

The burst response of Renshaw cells is due to short-latency, short-duration nicotinic receptors for acetylcholine, while tonic firing is attributed to weaker, persistent muscarinic receptors ( Curtis and Ryall 1966a–c). For a fairly constant level of motoneuron activity, the dynamic (nicotinic) response of Renshaw cells should
be more important than the tonic firing. The use of a single synapse to represent Renshaw cell activation should not invalidate the simulation results.

It has been reported that recurrent IPSPs on motoneurons may be mediated by γ-aminobutyric acid (GABA) as well as by glycine. Cullheim and Kellerth (1981) reported both glycine and GABA antagonists could reduce IPSPs from Renshaw cells, but neither antagonist alone could completely abolish recurrent inhibition. The putative GABAergic component of recurrent IPSPs had a smaller magnitude but a longer time constant than the glycinegic component. The hypothesis underlying this study was that weak inhibition can influence timing of spike firings, so it was necessary to consider the effect of changing the relative magnitude and time course of recurrent inhibition. This issue is described further in Sensitivity analysis.

Activation of motoneuron pool

Motoneurons normally receive many synaptic inputs, so that even a steady input contains a significant degree of membrane noise superimposed on an average baseline current. In the simulations, we specified both a steady-state current to provide the baseline and added to this a stochastic input to simulate the noise. The steady-state current input was added to motoneurons according to size, following a distribution used by Heckman and Binder (1993). This distribution can produce realistic rate limiting of motoneurons, and one of the goals of this study was to observe motoneuron-Renshaw cell interactions under realistic conditions. The input current was divided into two components, a “low” component weighted on smaller motoneurons and a “high” component weighted on larger motoneurons. The rationale is that Ia excitatory inputs are preferentially weighted on smaller motoneurons and rubrospinal inputs preferentially excite larger motoneurons.

As the total current input increased, an exponential crossover divided it into “low” and “high” components

\[
\text{input}_{\text{low}} = 6.5 \text{nA} \times \left[ 1.0 - \exp \left( -\text{input}_{\text{total}}/6.5 \text{nA} \right) \right] \tag{8a}
\]

\[
\text{input}_{\text{high}} = \text{input}_{\text{total}} - \text{input}_{\text{low}} \tag{8b}
\]

The weights were based on the relative position of each motoneuron, noted by the value of \( r_i \), as described in Eq. 1, along the exponential distribution of current thresholds. The weights were

\[
\text{weight}_{\text{low},i} = 1.6 - 0.8r_i \tag{9a}
\]

\[
\text{weight}_{\text{high},i} = 0.1 + 1.8r_i \tag{9b}
\]

where \( r_i \) is the same value used to define the neuron’s current threshold and related properties, and each motoneuron \( i \) receives excitatory current input of

\[
\text{input}_i = \text{weight}_{\text{low},i} \times \text{input}_{\text{low}} + \text{weight}_{\text{high},i} \times \text{input}_{\text{high}} \tag{10}
\]

Weights that varied linearly with current threshold rather than motoneuron index produced comparable results to those presented in this paper.

The stochastic component of the input was added once the steady-state amplitude was specified by the sum of the low and high components defined earlier. The stochastic inputs were generated by low-pass filtering the output of a random number generator. The amplitude of the stochastic input, defined as a percentage of the square root of the steady-state current drive, was set to a value empirically determined to produce an average \(-0.15\) coefficient of variation of motoneuron interspike intervals, comparable with those seen in human upper limb (Andreasen and Rosenfalck 1980). The scaling of the stochastic input was based on the observation that for a filtered white noise input, the variance is proportional to the mean (Papoulis 1984). The same modulation of the current drive was applied to all motoneurons simultaneously.

The bandwidths used were 2 Hz, to represent changes in common drive to the motoneurons in the pool (cf. DeLuca and Erim 1994); 50 Hz, to represent the synchronizing effect of EPSPs, assumed to have a time course of a few milliseconds, arriving simultaneously on the same motoneurons; and 10 Hz, as an intermediate value. For comparison, Allum et al. (1978) reported that the power spectra of low-frequency fluctuations in the net activity of the motor pool and higher-frequency activity of unfused or partly fused twitches of motor units overlapped at 6–12 Hz.

Number and length of trials

During a simulation run, 60 motoneuron pools were generated randomly, 10 at each mean activation level of interest (15, 18, 21, 24, 27, and 30 nA), according to the exponential distribution for current thresholds described previously. This eliminated the possibility that the observed effects of Renshaw cells were due to any particular arrangement of motoneurons within our grid. Each pool’s behavior was examined before and after the recurrent inhibitory feedback loop was closed. The stochastic input to the motoneuron pools was different for each trial, although the same bandwidths and amplitudes were used.

Each trial consisted of an initial 1 s to allow the simulation to reach a steady state and then 4.608 s, from which statistics were calculated. The integration step used was 0.5 ms, although a 1-ms time bin was used to calculate statistics of motoneuronal firing.

Estimates of synchrony

After the initial portion of the simulation trial, 10 motoneurons that had fired at least four times were selected randomly as reference units. During the steady-state portion of the trial, individual firing times of those 10 units were saved by the program. These 10 units were considered the reference units for calculation of synchrony. At the end of the simulation, the summed firing activity of the motoneuron pool was filtered by a triangular averaging window of 11 ms width to detect the short-term synchrony observed by Dietz et al. (1976).

For each reference unit \( j \), a synchrony coefficient was calculated as

\[
\text{synch}_j = \frac{1}{N_j} \sum_{l=1}^{N_j} w(\tau_l, j) m_l(t) \tag{11}
\]

where \( T \) was the length of the steady-state portion of the trial (4.608 s, in 1-ms bins); \( m_l(t) \) was the time series representing the total firing activity of the motoneuron pool minus the contribution of the reference unit \( j \); \( N_j \) was the total number of times the reference unit had fired over the trial; and \( w(\tau_l, j) \) is the averaging window centered at individual firing times \( \tau_l \) of the reference unit. The coefficients of \( w \) were \([1, 2, 3, 4, 5, 6, 5, 4, 3, 2, 1]/36\).

If the average number of population firings per firing of the reference unit (numerator) was equal to the average number of population firings at any millisecond (denominator), the value of the coefficient was zero. This synchrony coefficient is analogous to a spike-triggered average of aggregate pool activity with respect to the reference motoneuron \( j \). Such a synchrony measure is relatively robust to changes in the width or shape of the cross-correlation peak (Harrison et al. 1991).

Calculation of power spectra

If oscillatory components were present in the pool motoneuron activity, they would not necessarily be visible in the noisy time
series. The power spectrum, a plot of average power in the time series versus frequency, would show periodic or quasiperiodic oscillations as peaks.

To measure the statistical relationship between driving input and motoneuron activity, which might be modified by recurrent inhibition, the coherence function was used (Bendat and Piersol 1988). (Coherence can be seen as a frequency-based correlation function between input and output.) A coherence of 1.0 at a given frequency means that the output is solely a function of the input. Coherence of <1.0 can mean the system either contains random noise or is contributing something to the output which is not a product of the input. In this study, coherence was used to examine both how recurrent inhibition affected the input-output behavior of the motoneuron pool and how mutual inhibition between two Renshaw cell populations might produce interactions between their associated motoneuron pools.

A trial length of 4,068 points was used to allow calculation of power spectra by nine 1,024-point fast Fourier transforms (FFTs), data segments overlapping by 512 points. Before the FFTs were calculated, each data segment had its mean subtracted and was multiplied by a Hanning window to counter the “picket-fence” effect (Bendat and Piersol 1988).

RESULTS

Activation of Renshaw cells

Despite the substantial nonlinear scaling between motoneuron size and Renshaw cell excitation, average Renshaw cell firing rates varied linearly with average motoneuron firing rates across all examined levels of activation ($r^2 > 0.99$, Fig. 1A). The greater effect of large motoneurons on Renshaw cells was apparent when recruitment alone was assessed. There was a systematic and visibly nonlinear increase of Renshaw cell firing with recruiting over that range where recruitment was increasing (Fig. 1B), but the linear correlation coefficient ($r^2 > 0.94$) was still quite high. For total pool activity, defined as motoneuron firing rate times fraction recruited (Fig. 1C), the relation between Renshaw cell firing and pool activation was again highly linear ($r^2 > 0.99$).

This linearization may be due to the exponential distribution of motoneuron current thresholds, described in METHODS, which weighted the motoneuron population to lower current threshold values. It also may be due to the shunting effect described by Cleveland et al. (1981), producing a less-than-linear increase in Renshaw cell firing with motoneuron activity that counteracted the more-than-linear effects due to scaling of Renshaw cell excitation with motoneuron size. It is consistent with observations that submaximally activated Renshaw cells are linearly dependent on the firing rate and number of stimulated motor axons (Ross et al. 1972, 1982).

Inhibition of motoneurons

INHIBITION OF THE POPULATION ACTIVITY. Figure 2A plots the net change in average motoneuron pool firing rate produced by Renshaw feedback (ordinate) against the average firing rate observed without the feedback. The suppression of motoneuron firing rates increased with the average motoneuron firing rate. This is consistent with the experimental results of Granit and colleagues (Granit and Renkin 1961; Granit et al. 1960).

Figure 2B plots the net change in recruitment against the percentage of motoneurons recruited without recurrent inhibition. The Renshaw-mediated change in motoneuron recruitment did not visibly change with the level of recruitment or the average firing rate of the motoneuron pool. Presumably, this is due to a fixed number of motoneurons being just above threshold at each tested level of motoneuron activity.

The small changes in both firing rate and recruitment indicated that the effective loop gain of recurrent inhibition should be small. As a test of this, we calculated a direct estimate of Renshaw cell loop gain. Because the same pools were examined in the presence and absence of recurrent inhibition and received the same mean input, the effects of the Renshaw cell loop on the static gain of motoneuron firing
motoneuron size (Fig. 3) all three input bandwidths (range 0 of motoneurons recruited. show peaks where the motoneurons fired and valleys where Renshaw cell feedback. Motoneurons activated with 10-Hz bandwidth ten showed that coefficient of variation would increase with

of recruitment. chrony estimate, depends on two quantities. One is the sum bin for all motoneurons, i.e., $A$ defined as the average number of spikes fired per millisecond of the summed motoneuron firing. If the motoneurons fired with recurrent inhibition. Average motoneuron activity was population was estimated using the coefficient of variation

$B$: recurrent inhibitory reduction of recruitment is not dependent on level of recruitment. Ordinate: recruitment with Renshaw cell feedback minus recruitment without Renshaw cell feedback. Abscissa: recruitment without Renshaw cell feedback. Data from same simulation trials as in A. At the highest levels of activation, Renshaw cell feedback did not produce a change in recruitment; data points at $x = 100\%$ recruitment, $y = 0$ net change overlap.

could be estimated through simple subtraction. If recurrent inhibition behaved as a simple negative feedback system, then the average motoneuron output should have been attenuated by the factor $1/(1+GH)$, where $GH$ was the feedback normalized loop gain, a dimensionless number. $GH$ therefore could be estimated as

$$GH = A_0/A_1 - 1.0 \quad (12)$$

where $A_0$ was the average motoneuron activity without recurrent inhibition and $A_1$ was the average motoneuron activity with recurrent inhibition. Average motoneuron activity was defined as the average number of spikes fired per millisecond bin for all motoneurons, i.e., $A = \text{mean firing rate} \times \text{number of motoneurons recruited}$.

The average normalized loop gain estimate was 0.10 at all three input bandwidths (range $-0.01$–$0.17$, 2 Hz; $0.07$–$0.16$, 10 Hz; $0.07$–$0.12$, 50 Hz). This loop gain appears to be too small to accomplish any of the tasks associated with negative feedback systems, such as adjusting the gain of the system, reducing the sensitivity to transients, or increasing the bandwidth of the system (Houk and Rymer 1981; Marmarelis and Marmarelis 1978).

SIZE-DEPENDENT INHIBITION OF INDIVIDUAL MOTONEURONS. Recurrent inhibition had a greater effect on larger motoneurons (Fig. 3). Polynomials were fit to two data sets of motoneuron firing rate versus motoneuron current threshold (Fig. 3A), and the difference between them was used to estimate the decrease in firing rate from Renshaw cell feedback (Fig. 3B: heavy line). The greater inhibition on larger units might be a consequence of the scaling of voltage threshold with current threshold (see METHODS), but such a scaling would be linear with current threshold (Fig. 3B: thin, solid line). The function used to scale excitation of Renshaw cells with motoneuron size (Fig. 3B: thin, dashed line) shows a curvature qualitatively resembling the size-dependent inhibition of motoneurons.

Another possible mechanism for the size-dependent inhibition of motoneurons was suggested by the distribution of interspike interval (isi) statistics. Larger units tended to have larger coefficients of variation (c.v.) of the interspike interval than units recruited earlier. The larger coefficient of variation may be due either to larger effective currents on larger motoneurons via the “high” component (see METHODS) or to the closer proximity of larger motoneurons to their current thresholds, so that a downward swing of current would be likelier to silence the motoneuron firing completely. In the latter case, a larger motoneuron would presumably be more vulnerable to recurrent inhibition. To confirm this, motoneuron current threshold was plotted versus the coefficient of variation of the interspike interval. Although these plots often showed that coefficient of variation would increase with current threshold in a similar manner to the decline in firing rate, this was not the case at higher levels of motoneuron activation; an example is plotted in Fig. 3C, where the U-shaped plot of isi c.v. versus motoneuron firing threshold is clearly dissimilar to the consistently monotonic size-dependent inhibition of motoneurons.

The effect of Renshaw cells on the mean firing rate of motoneurons was apparently not dependent on the variability of firing of the motoneuron. The important factor, at least in this model, was the magnitude of excitation the motoneuron provided to neighboring Renshaw cells. In any event, the net effect on motoneuron firing rates was fairly small (a few pp's), on the same order of magnitude seen by Granit and colleagues when they enhanced Renshaw feedback by using motoneuron firing to trigger ventral root stimulation (Granit and Renkin 1961; Granit et al. 1960).

Renshaw cell effects on synchrony POPULATION SYNCHRONY. The overall synchrony within a population was estimated using the coefficient of variation of the summed motoneuron firing. If the motoneurons fired synchronously, then the summed motoneuron firing would show peaks where the motoneurons fired and valleys where they did not. The coefficient of variation of the time series formed by the total firing of the motoneuron ensemble would indicate the effect of the Renshaw cell on synchronous firings across the population.

Figure 4 shows that the coefficients of variation of the population firing tended to decrease as a function of average motoneuron firing rate (Fig. 4A) and increase with wider input bandwidth for the same motoneuron pool activity (Fig. 4B). When Renshaw cell feedback was present, the coefficients of variation were decreased, but only by a small amount (Fig. 4A; ○ vs. ●). As the input bandwidth increased, the change resulting from recurrent inhibition became even smaller.

The reduction of the variance of summed motoneuron firing by Renshaw cells was compatible with the hypothesis that recurrent inhibition reduces synchrony within a motor nucleus. The small size of the effect, however, further indicates that the role of the Renshaw cell is something other than the regulation of the total activity of a motor nucleus.

UNIT-TO-PopULATION SYNCHRONY. The variance of summed motoneuron firing, used above as an overall population synchrony estimate, depends on two quantities. One is the sum
of all possible covariances between pairs of active motoneurons, which we assume will be changed by recurrent inhibition. The other quantity is the sum of variances of individual motoneuron firing activity, which is not specifically of interest and which may be large enough to obscure the effect of recurrent inhibition. Therefore, we tested a synchrony measure (defined in METHODS) that was based solely on the cross-correlation between selected reference motoneurons and the rest of the motoneuron population. Each set of 10 trials at the same motoneuron activation regime (effective driving current, bandwidth, and presence or absence of recurrent inhibition) produced a population of 100 synchrony coefficients.

At each activation level, the average synchrony coefficient without recurrent inhibition was compared with the average synchrony coefficient after the recurrent inhibitory loop was closed. We had hypothesized that recurrent inhibition would decrease synchrony, defined as positive correlations near zero lag, between individual units. Instead, we observed no consistent relationship between the two cases (Fig. 5, bottom). The motoneurons driven at 2 and 10 Hz showed no consistent change, those driven at 50 Hz tended to become more correlated. The results also showed that whatever correlations between individual units and population firing existed before recurrent inhibition, their magnitude was small. The tendency of synchrony coefficients to small, negative values suggests that motoneurons in a pool have a lower probability of firing simultaneously than random chance.

FIG. 3. Renshaw cell inhibition of motoneuron firing as a function of motoneuron firing threshold. A: motoneuron firing rates before (heavy top line) and after (narrow bottom line) the recurrent inhibitory feedback is applied; 10-Hz bandwidth synchronizing input, mean firing rate 30 pps with Renshaw cell loop open, 27 pps with Renshaw cell loop closed; recruitment 100%. B: comparison of size-dependent inhibition to theoretical expectations. Difference between the 2 curves in A is calculated by polynomial fits to the data points (heavy line). Drawn for comparison are the expected differences if the Renshaw cell inhibition was due to the change in firing rate from systematic variations in threshold (thin, solid line) or from the scaling of Renshaw cell excitation with motoneuron size (dotted line). Two theoretical curves are scaled to the same initial point as the estimated difference. C: interspike interval statistics do not show same monotonic increase with motoneuron threshold as does inhibition of firing. Coefficient of variation (SD/mean) of the interspike interval of motoneuron firing (without Renshaw cell input), also plotted against motoneuron current threshold. Same trials as in A and B.

FIG. 4. Recurrent inhibition has little effect on population synchrony. A: population synchrony at 2 Hz is reduced by recurrent inhibition. Population synchrony is estimated as the coefficient of variation of the total number of motoneuron spikes in a 1-ms bin over the duration of the trial. Population synchrony without recurrent inhibition (∙) tends to be larger than that with recurrent inhibition (○) at the same firing rate. B: population synchrony at 10- and 50-Hz bandwidths is not as strongly affected. Tendency to synchronize, estimated from the magnitude of the population synchrony measure, also appears to increase with the modulation bandwidth. Population synchrony coefficients from trials at 10- and 50-Hz input bandwidth are plotted against coefficients from trials at 2-Hz input bandwidth and at the same level of activation of the motoneuron pool. Trials do not represent identical pools at each bandwidth; the individual trials are plotted instead of the averages to show the distribution of population synchrony coefficients.

FIG. 5. Effect of recurrent inhibition on unit-to-population synchrony coefficients. Left: motoneuron firing behavior during 2-Hz bandwidth synchronizing input; center: 10 Hz; right: 50 Hz. Unit-to-population synchrony coefficients for a specified level of motoneuron pool activation, synchronizing input bandwidth, and presence or absence of recurrent inhibition are averaged. Averages are plotted against average motoneuron firing rate (bottom 2 traces). At 2- and 10-Hz bandwidths, the average synchrony coefficient with the Renshaw cell loop closed (thick line) does not show substantial difference from the synchrony coefficient with the Renshaw cell loop open (thin line). At 50 Hz, recurrent inhibition increases synchrony coefficients, bringing them closer to 0 but still negative. When the SDs of the unit-to-population synchrony coefficients at each activation level were calculated, the closed-loop standard deviations (filled circles) tended to show a significant decrease from the open-loop standard deviations (open circles). Dashed lines bracket the 99% confidence region (n = 100 for both open and closed loop) around each estimate of the SD of the open-loop synchrony coefficients.
would predict, assuming that the motoneurons were independent random processes. The reason for the negative values was that although the interspike intervals show statistical variability, motoneurons tend to fire periodically and motoneurons of different sizes will fire at different rates. The differences in input scaling also will come into play, where motoneurons receiving a relatively small amount of mean drive will see a proportionately small statistical fluctuation in its input.

A routine statistical test led to a surprising but enlightening result. To validate the use of a Student’s t-test for comparing average synchrony coefficients, the F test was used to confirm that the variances of the synchrony coefficients were equal with and without recurrent inhibition. They were not equal (Fig. 5, top 2 traces). For 2 and 10 Hz bandwidths, the variance of the unit-to-population synchrony coefficients was less with the closed recurrent inhibitory feedback loop than with the loop open. Most closed-loop variance estimates fell below the 99% confidence interval of the variance estimated when no recurrent inhibition was present. This effect also was present at 50 Hz but only at the highest levels of activation tested.

If recurrent inhibition was only suppressing positive synchrony coefficients, then there would be a net decrease in the average of the synchrony coefficients. This decrease was not observed, although a change in the variance was seen. The implication was that recurrent inhibition was suppressing synchrony coefficients both greater and smaller than the average value of synchrony across the population. In other words, the Renshaw cell circuit was reducing both positive and negative correlations between motoneuron spike trains, so that decorrelation instead of desynchronization was the net effect.

**Renshaw cell effects on motoneuron power spectra**

Decorrelation of motoneurons should produce a visible change in the power spectrum of aggregate motoneuron firing (cf. Allum et al. 1978). The power spectrum describes how the variance of a time series is distributed across a range of frequencies. The variance calculated to produce the coefficients of variation plotted in Fig. 4 describes the net effect of the Renshaw cells across all frequencies, and this effect was seen to be small. This effect was found to be larger when considered in the context of a narrow, physiologically relevant frequency band.

Without recurrent inhibition, the power spectrum of simulated motoneuron firing showed a peak (Fig. 6). The magnitude of this peak increased with input bandwidth, consistent with the observation (Fig. 4) that population synchrony tended to increase with input bandwidth. Adding recurrent inhibition resulted in a marked attenuation of the peak in the frequency spectrum for each of the bandwidths and a shift of the peak frequency to the left.

The mean frequency of the motoneuron pool at each level of activation (Fig. 6; ●) consistently lagged the peak of the power spectrum. This relationship is explored in Fig. 7. The frequency of the highest amplitude point of the power spectrum was compared with both the average firing rate of the population and to the highest observed firing rates (Fig. 7A, ○ and *) observed during the averaged trials. Assuming that the frequency of the peak corresponded to motoneuron firing rates, the expected motoneuron firing rates for a given frequency are plotted as a dashed line. The better match was clearly between the frequency of the peak and the highest firing rates present. Furthermore, the units with the highest firing rates tended to be drawn from the middle of the active motoneuron population (Fig. 3A). This is because the smallest units were rate-limited by the input (see METHODS) and the largest units were recruited only recently. Therefore, the peak in the frequency spectrum probably represents the dominant firing rate of the motoneurons. Whether the spectral peak depends on rate-limiting is addressed when a homogeneous pool is considered in Sensitivity analysis.

In the absence of recurrent inhibition, the coherence between aggregate motoneuron activity and synchronizing common drive shows a dip at the frequency corresponding to the peak magnitude of the power spectrum (Fig. 7B and C). The improvement of coherence with Renshaw action (Fig. 7B) supports an earlier suggestion (Adam et al. 1978; Windhorst et al. 1978) that recurrent inhibition may improve the transmission of information through motoneuronal pathways. The decline of coherence at the frequency of the peak suggests that the peak arises due to intrinsic nonlinearities in the motoneurons, probably the transformation of inputs into discrete event trains. Decorrelation of motoneurons by Renshaw cells would diminish the effect of individual spike trains on the output power spectrum (see DISCUSSION), producing the increased coherence.

**Sensitivity analysis**

**INCLUSION OF DECORRELATING NOISE.** If the inputs to the motoneuron pool are routinely uncorrelated, the proposed
actions of the Renshaw cells would become unnecessary. The random component of the noise would counteract phase-locked relationships between individual motoneurons. To examine this possibility, the simulation was run with the common drive input to the motoneurons reduced by one-half, and an equal random input (at the same bandwidth) was administered to each motoneuron individually. Each motoneuron saw an input with the same bandwidth and power as when the inputs to the pool were totally synchronizing. Because of the effects of averaging, this produced a substantial decrease in the overall variability of the aggregate motoneuron firing, even though the variability of firing of each individual motoneuron was still ~0.15.

With this reduction of correlated input to 50%, the spectral peaks were reduced sharply. Renshaw cell action still could provide further attenuation, with a magnitude comparable to Renshaw cell performance during a fully correlated drive to the motoneuron pool (Fig. 8, A–C). It also produced comparable effects on the standard deviations of the unit-to-population synchrony coefficients (Fig. 8D).

SIMULATION OF THE SOLEUS MOTOR POOL. Recurrent inhibition is known to be prominent in the soleus motor nucleus (Eccles et al. 1961), which has a much narrower distribution of motoneuron sizes than the medial gastrocnemius (Burke 1981; Henneman and Mendell 1981). Recurrent inhibition presumably will have the same effect in both pools. A soleus motoneuron pool was approximated by keeping an exponential distribution of motoneuron sizes but restricting the range of current thresholds to 4.0–7.1 nA. All other aspects of the pool—number of neurons, statistical properties of input, distribution of excitation with motoneuron size, etc.—were the same as in previous simulations. As before, the effects of recurrent inhibition on spectral peaks and synchrony coefficients persisted.

In considering the size-dependent inhibition of Renshaw cells in RESULTS, we raised the possibility that such effects were due to size-dependent variations in any or all of the following: voltage thresholds of motoneurons, rate-limiting produced by the distribution of activation current to motoneurons, or excitation to Renshaw cells from motoneurons. Because of the restricted range of the soleus motoneuron pool, the voltage threshold and Renshaw cell excitation each only increase by 10% from smallest to largest motoneuron in the pool. As recurrent inhibition has the same effects on the restricted population as it did on the larger motoneuron pool, it can be concluded that these size-dependent variations are not important in the function of recurrent inhibition.

SIZE OF INHIBITORY CONDUCTANCE VERSUS SPATIAL EXTENT OR TIME COURSE. To determine how the selected values for neuronal parameters impacted on the performance of the model, one of the three key parameters describing the inhibitory synapses from Renshaw cells—either the magnitude or the time constant of the inhibitory conductance or the rostrocaudal distribution of synapses—was increased by 50%. One of the other two parameters then was decreased

**Fig. 7.** Spectral peak produced by periodic motoneuron firing varies with mean and peak motoneuron firing frequencies. A: frequency of greatest spectral amplitude varies with mean, peak motoneuron firing. Plot of the location of the spectral peak (before recurrent inhibition) as a function of mean firing rate is marked (□). Plot of the location of the spectral peak vs. the largest firing rate of motoneurons (see Fig. 3) active in the pool is marked (+). For comparison, the line y = x is drawn as a dashed line. Although both measures of motoneuron firing rate vary linearly with the peak frequency, the peak firing rate of motoneurons is clearly a better

**Fig. 8.** effects of recurrent inhibition persist in presence of desynchronizing inputs. A–C: suppression of peaks in motoneuron power spectra 10-Hz synchronizing input is used, matched with an equal amount of desynchronizing noise (average coefficient of variation of interspike interval for motoneurons ~0.15). Magnitude of the peaks in the motoneuron pool power spectrum before recurrent inhibition is smaller (A–C, increasing activation as in Fig. 6), but as before, the peaks shift to the right with increasing activation level and are suppressed by recurrent inhibition. D: Renshaw cell effects on unit-to-population synchrony coefficients, as in Fig. 5.
proportionally to preserve the average total recurrent inhibition. This was confirmed by calculating the normalized feedback gain as described earlier (under INHIBITION OF POPULATION ACTIVITY). This normalization made it possible to compare the relative effects of different synaptic parameters without altering the mean level of activity of either neuronal population.

When the trade-off was between magnitude of inhibition and its time course, it was seen that the weaker, longer-lasting IPSPs were less effective in suppressing the spectral peaks than the default values used in the previous simulations. The stronger, shorter-duration IPSPs were slightly more effective than the default values. When the trade-off was between magnitude of conductance and the rostrocaudal distribution of synapses, the suppression of the motoneuron spectral peak was the same as in the default case. We infer that the most important characteristic of recurrent inhibition is the time course of the IPSP and that should be short. The system is less sensitive to magnitude or rostrocaudal distribution of the IPSP conductances.

To confirm the relative effects of spatial extent and synaptic time constant, the trade-off between the two was examined directly. We found that longer-lasting, more narrowly distributed IPSPs were less effective than shorter-duration, more broadly distributed ones. A similar dominance of time course over rostrocaudal distribution was seen when the excitatory synapses from motoneurons to Renshaw cells were similarly modified.

EFFECTS OF INHIBITORY LINKAGES BETWEEN RENSHAW CELLS LINKING TWO SIMILAR MOTONEURON-RENSHAW CELL SYSTEMS. Substantial mutual inhibition between Renshaw cells excited by separate motoneuron pools may exist (Ryll 1981), and an explanation of recurrent inhibition has to be able to account for these connections. In each trial, two motoneuron pools were generated randomly and each connected to a separate population of Renshaw cells. The two pools of Renshaw cells were linked by powerful, broad mutual inhibition. Each Renshaw cell in one pool could inhibit 63 Renshaw cells in the other pool, spatially weighted as described in METHODS. The inhibitory synapse between Renshaw cells was four times as large as the magnitude of conductance of the IPSPs on motoneurons. These parameters were based on the extent of Renshaw cell axons beyond the synaptic contacts on motoneurons (Jankowska and Smith 1973; Ryall et al. 1971) and on the greater number of glycnergic receptors on Renshaw cells than on motoneurons (Fyffe et al. 1993). The reversal potential and the time course of the inhibitory conductance were the same for inhibitory synapses from the Renshaw cells to the motoneurons and from the Renshaw cells to the opposite Renshaw cells. The mutual inhibition produced was enough to decrease Renshaw cell firing rates by one-third.

The two pools each received as synchronizing inputs two independent, identically distributed, bandlimited stochastic processes. Inputs to motoneurons within a pool were correlated as before. Each pool received Renshaw cell feedback from its associated population as in the previous, single-pool simulations. Again taking the summed motoneuron firing of each pool as a time series, the coherence between the activity of each pool was calculated as described in METHODS. In the absence of inhibition between the Renshaw cell pools, the coherence between the summed firing of the two motoneuron pools was low and remained relatively constant across a broad range of frequencies (Fig. 9A, thin line). When mutual inhibition was added, coherence between pools increased substantially for frequencies corresponding to the range of individual motoneuron firing rates (Fig. 9A, thick line). This indicates that firing rates across the two pools were phase-locked. (It should be noted here that this in no way contradicts the results of Fig. 7B. In 7B, the coherence reflects the statistical relationship between drive to a motoneuron pool and the firing rates across the pool. In Fig. 9A, the coherence reflects the statistical relationship between 2 motoneuron pools.) To determine if the inhibition between the two Renshaw cell populations interfered with their decorrelating actions within their motor nuclei, the power spectra of individual motoneuron pools were calculated. For a broad range of firing rates and recruitment levels (<24 pps mean motoneuron firing rate, 99% recruitment) there was no increase in the spectral peak (Fig. 9B; note that the magnitude of the spectral peak is comparable to that seen in Fig. 6, for input frequencies of 10 Hz and intact recurrent inhibition). This indicates that inhibitory links between Renshaw cells can produce significant phase-locking between the overall firing activity of two populations of motoneurons, without interfering with the decorrelating effect of recurrent inhibition within each motor nucleus. Possible functions of this phase-locking are considered in DISCUSSION.

DISCUSSION

The simulation results presented in this paper agree with experimental observations that motoneurons receiving correlating inputs become phase-locked in the absence of Renshaw cell activity (Adam et al. 1978; Windhorst et al. 1978) and with the hypothesis that Renshaw cells should be able to affect firing times of motoneurons. These effects occurred even though the magnitude of recurrent inhibitory effects on...
motoneuron population firing was weak. The specific features of Renshaw cell effects on motoneuron firing synchrony were different from our expectations. We expected recurrent inhibition to desynchronize motoneurons by decreasing positive correlations at zero lag between spike trains. Instead, both positive and negative correlations were reduced so that the Renshaw cell effect is one of decorrelation, not just desynchronization. The net result was that recurrent inhibition had a potent impact on the power spectrum of the summed motoneuron output, greatly reducing a sharp peak phase locking of motoneuron firing rates.

Because of the necessary assumptions and simplifications in the construction of this model, it is not possible to consider the simulations in this paper as providing the definitive description of Renshaw cell actions. The results of our model do present a novel view of how the recurrent inhibitory system may function in the context of a single motor nucleus, and show that its effects may persist in a variety of operating conditions.

**Competition between large and small units**

The experimental findings of stronger Renshaw cell activation by larger motoneurons, and of larger IPSPs on smaller motoneurons, had suggested that recurrent inhibition may preferentially suppress smaller, weaker motor units as larger, stronger motor units were recruited (Friedman et al. 1981; Hultborn et al. 1988a,b). When measured in terms of effective synaptic current, recurrent inhibition was approximately equal in all motoneurons (Lindsay and Binder 1991). We assume the variation in recurrent IPSP with motoneuron size is primarily due to the effect of differences in motoneuronal input resistance.

The distribution of input from Renshaw cells to motoneurons in our simulation was adjusted to give equal recurrent inhibitory current in all motoneurons. Our results indicate that larger units, which produce the strongest activation of Renshaw cells, are the ones that receive the greatest impact from recurrent inhibition. These also would be the ones most recently recruited. This supports the notion that Renshaw cells provide “motor contrast,” to confine motoneuron responses to areas directly receiving stretch or other feedback (Brooks and Wilson 1959; Granit and Renkin 1961; Ryall 1970; Windhorst 1989), but it would be a relatively weak effect (only a few pps, see Fig. 3).

**Renshaw cells decorrelate, not desynchronize**

Decorrelation and desynchronization are not the same thing. Synchronization of activity between two time series is indicated by a significantly positive correlation coefficient. The presence of any relationship between two time series is indicated by a correlation coefficient significantly different from zero, positive or negative.

Based on the initial hypothesis that Renshaw cells desynchronize, we expected to see the mean synchrony coefficient be positive when motoneurons received a common drive without recurrent inhibition and fall to zero when the recurrent inhibitory loop was closed. Instead, the simulation results indicate that the Renshaw cells act to decorrelate, that is, to suppress nonzero correlations between motoneurons in either direction, i.e., positive or negative correlations.

The reduction of positive correlations was presumably due to the effect of motoneurons inhibiting each other via the Renshaw cells. The reduction of negative correlations was presumably due to the effect of motoneurons inhibiting each other via the Renshaw cells. The reduction of negative correlations indicates that somehow the Renshaw cells were producing recurrent inhibition to desynchronize motoneurons by decreasing positive correlations at zero lag between spike trains. Instead, both positive and negative correlations were reduced so that the Renshaw cell effect is one of decorrelation, not just desynchronization. The net result was that recurrent inhibition had a potent impact on the power spectrum of the summed motoneuron output, greatly reducing a sharp peak phase locking of motoneuron firing rates.

Because of the necessary assumptions and simplifications in the construction of this model, it is not possible to consider the simulations in this paper as providing the definitive description of Renshaw cell actions. The results of our model do present a novel view of how the recurrent inhibitory system may function in the context of a single motor nucleus, and show that its effects may persist in a variety of operating conditions.

**Whitening of the power spectrum**

As described in Methods, the motoneuron pool activity studied in the simulation was depicted as the summed activity of 256 quasiperiodic units. Christakos (1986) demonstrated that the combined activity of a population of independent, quasiperiodic random processes—such as neuronal firings—will show a spectral peak such as the one seen in these simulations. The power spectrum of the sum of random processes will be the sum of the power spectra of each process and of the real parts of all of the possible cross- spectra. If the processes in the ensemble are all quasiperiodic with the same mean frequency, it is not necessary for them to be correlated for a prominent peak in the power spectrum to emerge. Thus even though the overall synchrony among our simulated motoneurons was low, there was a sharp peak in the power spectrum for the sum of motoneuron firings patterns (e.g., Fig. 6).

The decorrelation due to the Renshaw cell feedback was especially effective in reducing the peak of the power spectrum (again, see Fig. 6). Theoretically, there are two ways to reduce the contributions of the cross-spectra. An obvious solution to the problem would be to produce a 180° phase shift between two halves of the motoneuron pool. The out-of-phase components would sum and cancel. An alternative solution would be to produce a 90° phase shift between units. At 90° phase shift, cross-spectra are wholly imaginary and therefore would not contribute to the overall power spectrum. (One way of seeing this is to consider the correlation coefficient between 2 identical sine waves. If there is a 180° phase shift between the sine waves, the correlation coefficient is −1. If there is a 90° phase shift between them, the correlation coefficient is 0.)

Koehler and Windhorst (1985) saw in their model that recurrent inhibition, too small to impact the gain of motoneuron firing, would produce a phase-shift of 90° between S and combined FR and FF populations. When a homogeneous distribution of Renshaw cell inhibition was assumed, as in the current model, the FF lagged the S motoneurons by 90°, and the FR motoneurons showed an intermediate phase lag. In the current study, it was not feasible to calculate phase shifts between pairs of units. The reduction of the peak in the power spectrum of motoneuron population activity observed in the current study was consistent with the phase shifts predicted by the Koehler and Windhorst model.

Far from being “weak,” recurrent inhibition appears to be a powerful way to adjust the dynamic behavior of a
neuron population with minimal impact on its static gain. We write "neuron" instead of motoneuron as there are other regions in the CNS where lateral or recurrent inhibition is present and they may work along the same principle.

Possible effects on the development of physiological tremor

Increased occurrences and larger magnitudes of positive correlations between motor unit firings have been associated with observations of large amplitude tremor in human subjects (Dietz et al. 1976). No inquiry has been made into the distribution of negative correlations under these conditions. This result is consistent with the findings of Dietz et al. (1976) and makes a further prediction: if a similar experiment to that of Dietz et al. looked for statistically significant correlations between pairs of motoneurons and counted both positive and negative correlations, it would find that at higher levels of physiological tremor, both positive and negative correlations are larger and more frequent.

Synchronous and asynchronous stimulation of ventral root bundles both produce a peak in the force spectrum at the stimulus rate peak (Allum et al. 1978). The asynchronous stimulation attenuates the peak in a manner comparable to the reduction of the peaks in the motoneuron power spectra by Renshaw cells in the current model. If the motoneuron synchrony associated with tremor was reduced by recurrent inhibition in the manner indicated by this study, then less frequent significant correlations—positive or negative—would be observed.

We assume that the motoneuron population firing behaviors described in this paper will contribute to this tremor, although the question is by what mechanism. Synchrony on the order of 10 ms may not be meaningful on the much longer time scale of motor-unit twitches. The low-pass filtering properties of muscle suggest that the periodic motoneuron pool activity suppressed by the Renshaw cells would have little effect on the force output. On the other hand, Rack and Westbury (1969) observed that asynchronous stimulation of ventral root filaments produced both smoother and larger force output than did synchronous stimulation. This effect would be produced through nonlinear summation of motor unit twitches: adjacent muscle fibers, contracting simultaneously, might produce less total force than the sum of the individual twitch forces. It should be noted, though, that the division of ventral roots into ten or so filaments to produce "asynchronous" stimulation (Allum et al. 1978; Rack and Westbury 1969) still will produce substantial synchronization due to the number of simultaneously active motor units within each filament. Whether Renshaw cell effects can impact force generation directly may have to be tested by incorporating a muscle model incorporating the full range of muscle mechanical nonlinearities.

An indirect but still powerful pathway for the oscillatory component in the motoneuron power spectrum to produce tremor is through proprioceptive loops. Both muscle spindle and Golgi tendon organ afferent responses have high-pass properties (reviewed in Prochazka 1996), which could counteract the low-pass filtering from muscle. Entrainment of Type Ia, Ib, or II afferents by quasiperiodic motor unit population activity may contribute to physiological tremor. The covariance of Ia afferents and recurrent inhibition has been noted elsewhere (Baldissera et al. 1981). The need to "pre-filter" motor unit activity to prevent entrainment of afferents may be a reason for this covariance. Illert et al. (1996) suggest, given that recurrent inhibition is weak or absent in distal motor nuclei and absent in amphibians, that the role of the Renshaw cell is to maintain posture. Stabilization of reflex loops, via suppression of the peaks in the motoneuron power spectra, would be a mechanism by which the Renshaw cell could assist in postural control.

Will mutual inhibition between Renshaw cell populations synchronize motor nuclei?

If the role of Renshaw cells is to decorrelate motoneuron firings within a motor nucleus, it would follow that the role of inhibition between Renshaw cell populations is to produce correlations in population activity between their associated motor nuclei. When agonist motoneurons fire, antagonist motoneurons would be disinhibited and thus also tend to fire. Such inhibitory linkages between Renshaw cell populations have been found to occur between functional antagonists (Ryall 1981).

Inhibition of Ia inhibitory interneurons by Renshaw cells (Baldissera et al. 1981), which would produce a further disinhibition of antagonists, may further contribute to the between-muscle correlating effect. Ia inhibitory interneurons were not considered in the current model because of the lack of information needed to model them in the same detail as the motoneurons and Renshaw cells.

The functional role of the Renshaw cell-mediated enhancement in correlation between separate motoneuron pools might be as follows. Consider first a muscle acting in isolation. Decorrelation of motoneurons within a motor pool may attenuate tremor by causing motor units to sum their forces out of phase. This would help minimize tremor. Now consider the case for two antagonist muscles acting at across a single joint. Out-of-phase firing in motoneurons in one muscle in comparison to the other would tend to increase net joint tremor. If motor units between the two pools were correlated, even though motor units within each pool were uncorrelated, then unfused contractions of motor units pulling in opposite directions would sum and cancel. Such synchronization may result from mutual inhibition between Renshaw cells considered in Sensitivity analysis.

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REFERENCES

Adam, D., Windhorst, U., and Inbar, G. F. The effects of recurrent inhibition on the cross-correlated firing patterns of motoneurones (and


Lagerback, P.-Å. and Kellert, J.-O. Light microscopic observations on Renshaw cells after intracellular staining with horseradish peroxidase.


