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Bilateral Soleus H-Reflexes in Humans Elicited by Simultaneous Trains of Stimuli: Symmetry, Variability, and Covariance

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Mezzarane, Rinaldo A. and André F. Kohn. Bilateral soleus H-reflexes in humans elicited by simultaneous trains of stimuli: symmetry, variability, and covariance. *J Neurophysiol* 87: 2074–2083, 2002; 10.1152/jn.00129.2001. Experiments using electrical and mechanical activation of spinal reflexes have contributed important results toward the understanding of neuronal and synaptic dynamics involved in spinal neural circuits as well as their response to different inputs. In this work, data obtained from the simultaneous stimulation of both legs are analyzed to provide information on the degree of symmetry of the respective spinal reflex circuits and on the characteristics of reflex variability. H-reflexes recorded from relaxed muscles show a frequency-dependent amplitude depression when elicited by a train of stimuli. This effect has been attributed to homosynaptic depression. Soleus H-reflexes were recorded in response to trains of simultaneous stimuli applied to both legs in right-handed subjects that were sitting in a relaxed state. The first objective was to verify the existence of asymmetries in H-reflex parameters obtained from the two legs. We measured the mean, variance, and coefficient of variation of the depressed H-reflex amplitudes and the time constant of decay toward the depressed plateau. The second objective was the analysis of the time correlation of subsequent H-reflex amplitudes in a long train of responses recorded from a given leg. The statistical dependence of H-reflex amplitudes in the long trains recorded from both legs was also investigated. Data obtained from preliminary experiments showed that there was no effect of a given stimulus on the contralateral leg applied simultaneously or 1 s before, therefore validating the simultaneous stimulation paradigm. Paired *t*-tests indicated that several parameters measured bilaterally from soleus H-reflex trains of right-handed subjects were not statistically different in the overall, although individually there were statistically significant asymmetries, toward either the right or left leg. Sequences of H-reflex amplitudes, as measured by the auto-covariance, were either white or had a memory ranging from 2 up to 50 s. This indicates that the random fluctuations in presynaptic inhibition and/or postsynaptic inputs to motoneurons may have either fast or slow time courses. The average auto-covariance sequences of the right and left legs, computed from all subjects, were practically superposable. The cross-covariance between the bilateral H-reflex amplitudes showed a statistically significant peak at zero lag in some experiments, suggesting a correlation between the synaptic inputs to the Ia-motoneuron systems of the soleus muscles of both legs.

INTRODUCTION

The H-reflex is a useful tool in studies of human spinal cord neurophysiology and neuropathology. Changes in H-reflex amplitudes may occur due to modulation of presynaptic inhibition of Ia terminals, varying barrages of postsynaptic potentials on motoneurons, and homosynaptic depression in the Ia to motoneuron synapses. Presynaptic inhibition of Ia terminals has been shown to vary in different tasks (Faist et al. 1996); postsynaptic potentials on motoneurons increase or decrease their excitability and hence alter the reflex excitability (Goulart et al. 2000). Low-frequency trains of stimuli to the Ia afferents cause a depression of the reflex amplitudes (Katz et al. 1977; Taborikova and Sax 1969) that is probably due to homosynaptic depression in the Ia to motoneuron synapse (Hultborn et al. 1996; Kohn et al. 1997). During any behavior, a combination of factors such as those mentioned in the preceding text contributes to reflex modulation and to motor control.

Studies of H-reflex depression offer substrates for the understanding of neuronal and synaptic properties in the ventral horn as well as for the evaluation of neuronal circuit disorders that affect the segmental system (Crone and Nielsen 1989; Floeter and Kohn 1997; Ishikawa et al. 1966; Jefferson and Schlapp 1953; Katz et al. 1977; Lloyd and Wilson 1957; Schindler-Ivens and Shields 2000; Taborikova and Sax 1969).

Contradictory results are found in the literature on the existence of an asymmetry in the H-reflex recovery curve (RC) obtained from both sides (e.g., right and left soleus) and whether an asymmetry of such (partially) depressed responses would correlate with the dominant side of the subject (Chandran et al. 1988; Goode et al. 1980; Nativ et al. 1989; Tan 1985a,b).

Different approaches have been used for the study of neural mechanisms behind motor dysfunction (Ashby and Wiens 1989; Aymard et al. 2000; Katz et al. 1992; Panizza et al. 1989; Pisano et al. 2000). In the case of spasticity, the H-reflex depression is significantly lower in spastic patients (Nielsen et al. 1995; Schindler-Ivens and Shields 2000; Voigt and Sinkjaer 1998), and hence an index could potentially be derived for diagnostic purposes (Aymard et al. 2000; Schindler-Ivens and Shields 2000).

The random fluctuations in H-reflex amplitude have been studied by many researchers to understand their characteristics and origins (Funase and Miles 1999; Gossard et al. 1994; Nozaki et al. 1995, 1996; Rall and Hunt 1956; Rudomin and Dutton 1969; Rudomin et al. 1969; Somjen and Heath 1966). Gossard et al. (1994) have concluded from their experiments with cats that both presynaptic inhibition of Ia terminals and postsynaptic effects on motoneurons were relevant factors be-

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hind the reflex variability, but correlated postsynaptic inputs having a greater importance. The analysis of the randomness of H-reflex amplitudes in humans may give information on the various synaptic inputs affecting directly or indirectly the motoneurons and the Ia terminal boutons and hence potential information on different normal and abnormal states associated with the spinal cord circuitry.

The present work analyzes the existence of symmetry in parameters measured from simultaneous trains of H-reflexes obtained from both legs of normal subjects. The parameters include the fully depressed H-reflex amplitudes ("plateau level"), the time constant of the decay toward the plateau level, and the coefficient of variation of the reflex amplitudes around the plateau.

Additionally, we analyze the auto- and cross-covariance sequences of H-reflex amplitude sequences recorded from both legs. With the auto-covariance analysis, we intend to verify if there is some correlation between subsequent H-reflex amplitudes in a given train, which can suggest the types of fluctuations acting on the Ia/motoneuron system. The cross-covariance analysis will indicate if there are correlated or common inputs modulating the soleus motoneuron pools and/or associated Ia terminals of the soleus muscles from the two legs.

METHODS

Subjects

Ten healthy subjects (3 female, 7 male), ages from 24 to 48 (28.8 ± 7.1, mean ± SD), gave a written informed consent. Preliminary experiments were done on a subset of five subjects. The procedures were approved by a local ethics committee. All subjects were right-handed. The handedness was established by Oldfield's (1971) Edinburgh questionnaire, with an additional emphasis on the use of the legs. In all experiments, starting about 3 PM, the subjects were seated in a comfortable reclining armchair in a very relaxed state, the head always at a standard position. The foot was not strapped (very little movement was usually seen) but similar results should be expected with a fixed foot (Kagamihara et al. 1998).

H-reflex recordings

The active surface electrode for the soleus recording was attached about 4 cm below the inferior margin of the two heads of the gastrocnemius muscle. The reference electrode for the soleus was at the Achilles tendon. The positions of the corresponding electrodes in the two legs were carefully matched from an anatomical point of view. The signals were amplified and filtered (5 Hz to 1 kHz) by a Nihon-Kohden MEB 4200 system. Its analog outputs were fed into a PC-based DataWave data acquisition and processing system that sampled each signal at a frequency of 5,000 samples/s.

Stimulation procedures

Two independent electrical stimulators from the MEB 4200 were used to stimulate the posterior tibial nerve of each leg with 1-ms current pulses. The cathode was at the popliteal fossa and the remote anode on the patella. A stimulus intensity was determined for each leg that caused an H-reflex amplitude equal to about 20% of the corresponding maximum M response amplitude, M_{max} (Crone et al. 1990). All the trains of stimuli used in the experiments were at 1 Hz.

PRELIMINARY EXPERIMENTS. These were designed to verify the assumption that in our experiments a single stimulus, or a train of stimuli, to a leg does not affect the other leg's responses. In a first experiment, a single stimulus was applied simultaneously to each leg. A control stimulus was applied to a given leg 15 s after or before the pair of conditioning-test stimuli. Fifteen trials were performed in this situation. A second experiment was carried out with a conditioning stimulus train having eight pulses followed by a test stimulus on the contralateral leg after 1 s. After 20 s, a control stimulus was delivered to the contralateral leg. Forty trials were performed in this paradigm. In both preliminary experiments, the trials were separated by intervals of 20 s. Both preliminary experiments were carried on both legs, i.e., conditioning the right and testing the left and vice-versa.

ASYMMETRIES OF PARAMETERS FROM BILATERAL H-REFLEXES. For the purpose of evaluating the existence of asymmetries in the parameters from depressed H-reflexes, both legs received simultaneously 20 trains of 20 pulses each, making up a trial. The interval between the start of a train and the end of the previous was 20 s. Each subject had an average of three trials, the exact number depending on the course of the experiment (5 subjects had 4 trials, 4 had 3 trials, and 1 had 2 trials).

PARADIGM OF TRAINS WITH 500 PULSES. Trains of 500 stimuli at 1 Hz were applied simultaneously to each leg, followed by a replication obtained ≥30 s after the end of the first train. For two subjects (*S3* and *S6*), this experiment was repeated on a different day. This paradigm was designed for the studies of auto-covariance in single trains of H-reflexes and cross-covariance between simultaneous trains obtained from both legs.

Signal processing and data analysis

Data files in ASCII generated by the signal acquisition system were processed by programs written in Matlab (MathWorks). The procedures used in the quantification of the trains of 20 H-reflex amplitudes are described in the following text, while those for the trains of 500 H-reflexes are presented together with the results.

ASYMMETRY OF DEGREE OF DEPRESSION. The *degree of depression of a given train* (each comprised of 20 reflex amplitudes obtained at a rate of 1 Hz) was defined as the mean of the last 15 H-reflex amplitudes (H_p) divided by the first H-reflex amplitude in the train (H_1). This means that only the fully depressed values of H-reflex amplitudes were used to quantify the degree of depression (Kohn et al. 1997). On the other hand, the *degree of depression for any given trial* was the mean degree of depression computed from all trains (20) in that trial. Finally, the *degree of depression associated with a given leg* of a given subject was the average of the degree of depression computed from all trials. In this way, each subject contributed with a single point in the graph of right leg versus left leg degree of depression (Fig. 2*A*). For conciseness, we shall indicate the degree of depression by H_p/H_1, a *normalized* H-reflex plateau level, either of a train, a trial or an average from all trials. An individual analysis of the ratios H_p/H_1 obtained from each trial of a subject was also performed, the data being shown in Fig. 3 by the circles.

An alternative way of measuring a degree of depression is by means of a value of the H-reflex recovery curve read at a certain interstimulus interval (e.g., 1 s). For comparison purposes with data from the literature, we also assessed the asymmetries in the normalized H response amplitude elicited by the second pulse in a train (H_2) with respect to H_1.

ASYMMETRY OF H-REFLEX AMPLITUDE VARIABILITY. The variability of the depressed H-reflex amplitude sequences from both legs of each subject was measured by the coefficient of variation (CV), which is the ratio of the SD and the mean. For this analysis, each H-reflex amplitude was normalized by M_{max} and not by H_1 because the latter has a variability that is of no interest in this analysis.

The variance of each train was found from the last 15 reflex amplitudes in the train of 20 reflex amplitudes normalized by the respective M_{max}. The variance in each trial was the mean of the variances of each train in the trial. Finally, the variance for each leg was calculated as the mean of the variances in each trial. The CV for

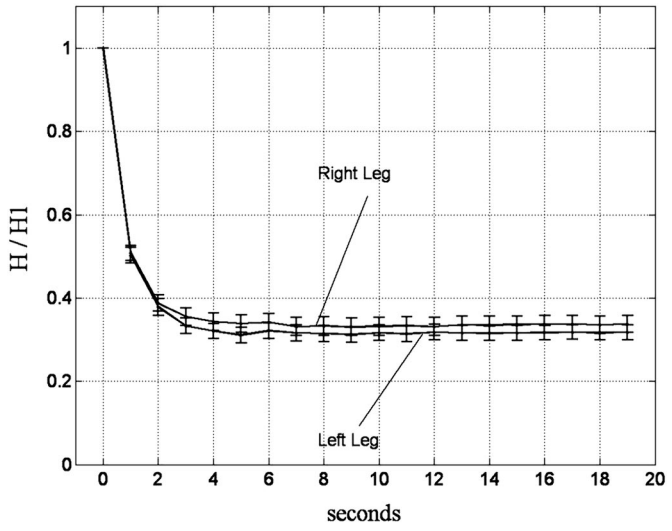

FIG. 1. Overall average time courses of the H-reflex amplitudes from the 2 legs in response to a bilateral train of 20 pulses at 1 Hz. The points for the right leg occurred slightly above those for the left leg. Time is plotted in the abscissa, and the H-response amplitudes normalized with respect to that of the 1st response are plotted in the ordinate. Adjacent points are joined by a straight line to aid in the visualization; the small vertical bars indicate SE.

each leg of a given subject was the SD (computed from the variance defined in the preceding text) divided by the corresponding mean of the plateau values (referred to M_{max}).

ASYMMETRY OF THE TIME DECAY OF RESPONSES. The time course of the mean amplitudes of H responses (trains of 20, all of them normalized by the respective H_1) computed from all the trials of each subject, from each leg, was fitted by an exponential function. As the time constant values were relatively small, and there was a residual variability in the reflex amplitudes, the reliability of the time constant estimate had to be assessed. A Monte Carlo simulation was run to estimate the error associated with each time constant value estimated from a trial's experimental data. This was done by generating many independent runs of sequences of a sampled exponential function with superimposed noise with parameter values similar to those obtained from the experimental train. The error was characterized by the coefficient of variation of the estimated time constants for each run. The criterion to consider a time constant value as reliable was that the coefficient of variation from the Monte Carlo simulation was less than 0.15 (i.e., a relative error smaller than 15% relative to the mean). Only 4 of 34 pairs of time constant values were rejected by this criterion. Therefore for any subject, only the trials that gave a reliable time constant estimate were used to compute the final time course of H-reflex amplitudes that yielded a time constant value used in Fig. 2*C*. In opposition to this parametric approach for each subject, we also computed the overall H-reflex decay for the right and left legs in our sample of subjects (Fig. 1).

STATISTICAL ANALYSIS. A two-sided paired *t*-test at a significance level of 95% was applied in all cases. In the preliminary experiments it tested if there was a difference between conditioned and control responses (expressed in $\%M_{max}$). In the main experiments, it tested the existence of asymmetries in parameter values obtained from the two legs.

To give a measure of compactness of the data obtained from our population of normal subjects, a bivariate normal approximation was computed from the 10 data points in each graph of Fig. 2 using the corresponding sample means and SD of the right and left leg values as well as the sample correlation coefficient. The 95% area defined on the right leg-left leg plane consists of an ellipse determined by a χ^2 value of 5.99 (Mardia et al. 1979). Each ellipse, centered at the

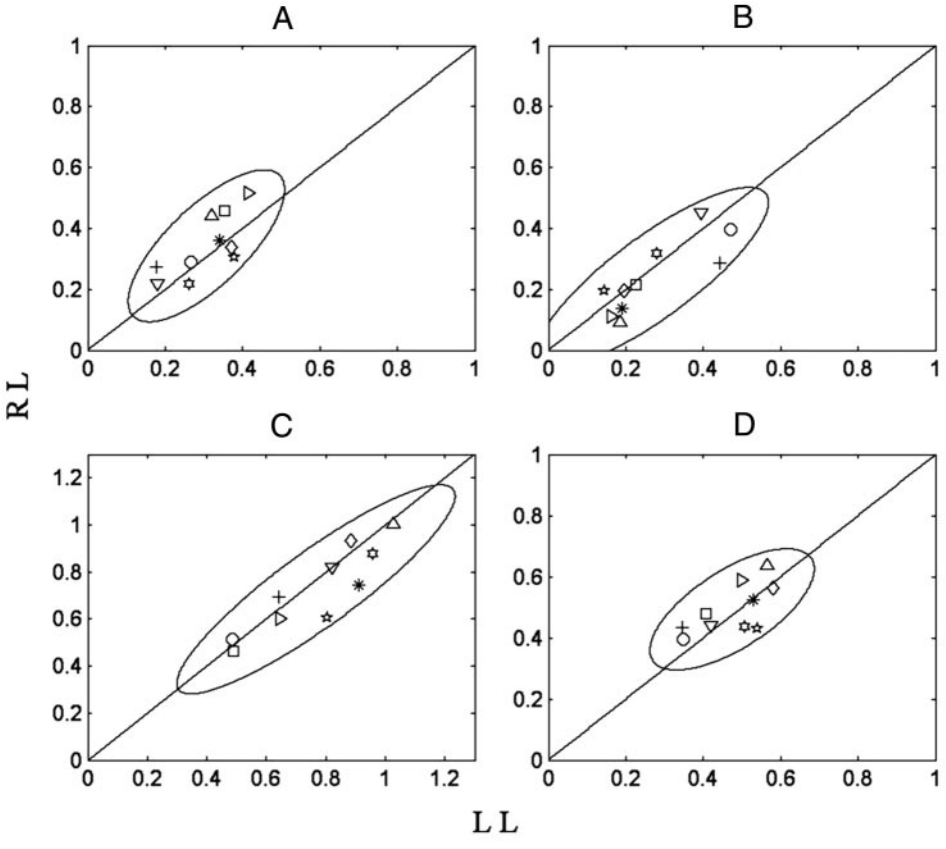

FIG. 2. Right leg (RL) vs. left leg (LL) H-reflex parameters for a population of 10 right-handed subjects. The ellipse indicates the 95% region estimated from the cluster of points assuming a bivariate normal distribution. *A*: H_p/H_1; *B*: CV of H-reflex amplitudes around the plateau value; *C*: time constant of decay toward the plateau, measured in seconds; *D*: H_2/H_1. ✳, *subject S1;* ○, *S2;* +, *S3;* △, *S4;* □, *S5;* ✡, *S6;* ◇, *S7;* ▽, *S8;* ☆, *S9;* ▷, *S10.*

coordinates of the mean values of right and left leg data points, is drawn together with the corresponding sample points.

RESULTS

Preliminary experiments

No statistically significant difference was found between control H-reflex amplitude and H-reflex amplitude conditioned by a train with eight pulses applied to the contralateral leg 1 s before the test stimulus (paired *t*-test, $P = 0.86$ and $P = 0.80$, for right and left legs, respectively). The same result was found when the H-reflex was conditioned by a simultaneous contralateral single pulse ($P = 0.24$ and $P = 0.44$, for right and left legs, respectively). These results suggest that there are no contralateral influences on the H responses when trains of stimuli (with the intensities used here) are delivered simultaneously to both legs.

Asymmetries of parameters from bilateral H-reflexes

Very rarely (in 26 of 680 trains) there were H-reflex amplitudes during a train that exceeded the respective H_1, thus interfering with the data analysis. These were probably associated with a considerable departure from the subject's relaxed control state, and the whole corresponding train was discarded from the analysis.

Overall means of the right and left leg sequences of H-reflex amplitudes are shown in Fig. 1 (±SE). The two time courses are relatively similar, the right leg responses being slightly above those of the left leg. The estimated time constants were 0.76 and 0.79 s for the right and left leg H-reflex amplitude sequences, respectively. Therefore in the overall, the transition from control reflex amplitudes to the plateau due to depression looks similar in the two legs in a population of right footed subjects (see also Fig. 2*C*).

A quantitative analysis of some parameters associated with the trains of H-reflex amplitudes is pursued in the following. The parameters were the degree of depression (H_p/H_1 and H_2/H_1), the reflex amplitude variability around the plateau value and the speed of decay of the reflex amplitude to the depressed amplitude plateau.

The 95% probability ellipses of the bivariate normal approximations are drawn in Fig. 2, the interpretation being that the probability of a point falling outside the ellipse is 0.05 (in Fig. 2*B* the ellipse is drawn truncated because the CV cannot be negative). This gives an idea of how much asymmetry could be accepted for a data point so that it is still considered as belonging to the control population. Additionally, the area that falls outside the ellipse could characterize subjects different from the control population of right footed healthy subjects, e.g., patients with some neurological disorder. Within this context, it is relevant to remember that in some pathologies, both limbs could be affected, although in different ways or degrees (Aymard et al. 2000; Sinkjaer and Magnussen 1994; Thilmann and Fellows 1991).

The points obtained from the 10 subjects corresponding to H_p/H_1 are shown in Fig. 2*A*. The large axis of the ellipse is steeper than 45° because the SD of H_p/H_1 for the right leg was larger than for the left. The correlation coefficient for these data was 0.74 ($P < 0.05$). The mean ± SD for the right leg was 0.34 ± 0.10 and for the left, 0.31 ± 0.08. The values for the mean plateau levels are similar to those obtained from Fig. 1.

The CV data points of right and left legs (Fig. 2*B*) showed a correlation coefficient 0.83 ($P < 0.05$). The mean CV values for the right and left legs were, respectively, 0.24 ± 0.12 and 0.27 ± 0.12. The dependence of the H-reflex amplitude variability on the size of the plateau level in the population was quantified by linear regression. The relation of H-reflex amplitude variance versus mean plateau level (referred to M_{max}) in the population was fitted by the regression lines $0.0027 \times H_p/M_{max} + 0.0002$ (correlation coefficient $r = 0.29$) and $0.0038 \times H_p/M_{max} + 0.0001$ (correlation coefficient $r = 0.55$) for the right and left legs, respectively. The relation of H-reflex amplitude CV versus mean plateau level was fitted by the regression lines $-2.59 \times H_p/M_{max} + 0.46$ (correlation coefficient $r = -0.64$, $P < 0.05$) and $-2.46 \times H_p/M_{max} + 0.45$ (correlation coefficient $r = -0.69$, $P < 0.05$) for the right and left legs, respectively. These two regression lines are practically superposable. The good linear fit with a negative slope line of the CV as a function of the plateau level has also been found in cat experiments by Somjen and Heath (1966), but they did not compare data from the two hindlimbs.

The mean computed from the time constant data points of Fig. 2*C* for the right leg was 0.73 ± 0.18 s and for the left leg was 0.77 ± 0.19 s and hence, in the overall, the time decays of the H-reflex amplitudes in the trains were similar in both legs, as also suggested by Fig. 1. These mean values were quite close to those obtained from Fig. 1, although they were computed differently. The correlation coefficient for the data points in Fig. 2*C* is 0.90 ($P < 0.05$).

For the H_2/H_1 data points in Fig. 2*D*, the correlation coefficient was 0.67 ($P < 0.05$) and the mean values were 0.49 ± 0.08 and 0.47 ± 0.09 for the right and left legs, respectively.

The differences in the degree of depression (as measured by H_p/H_1 and by H_2/H_1), reflex amplitude variability and time constant between right and left legs found in our population of subjects (Fig. 2) did not reach statistical significance ($P = 0.13$, $P = 0.22$, $P = 0.17$, $P = 0.40$, for Fig. 2, *A–D*, respectively). This suggests that in our population there was no asymmetry in the parameter values, and hence handedness does not seem to have an observable effect on them.

After the foregoing analysis of the behavior of a population, the data were examined for each subject. For example, in Fig. 2*A* there are seven subjects with less depression in the right leg and three with more depression on the right leg. As each subject had individually some asymmetry in the average values, we wanted to investigate whether the means of the trials of that subject (each had 3 trials on average, each based on 20 trains of H-reflexes) showed the same degree and direction of asymmetry as the subject's overall mean. Figure 3 shows thin and thick horizontal line segments that are the mean values for the right and left leg of a given subject, respectively (these represent the same data as in Fig. 2*A*). Additionally, Fig. 3 also shows the results from each subject's trials, the empty (filled) circles corresponding to the right (left) leg H_p/H_1 computed in the trial and the arrows indicating a nonsignificant difference between right and left leg values. For example, the first subject had two trials; in both, the right leg had a higher normalized plateau level than the left, but only in the second trial was the difference between legs statistically significant. The second subject had the right leg with a higher normalized plateau level

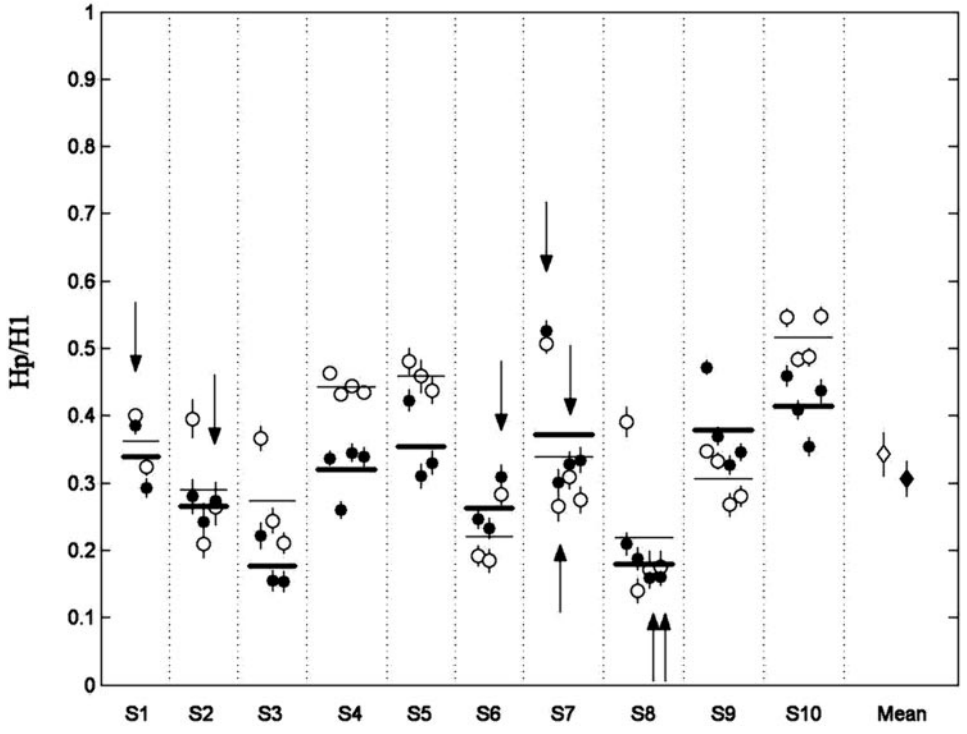

FIG. 3. H_p/H_1 for each subject (*S1–S10*) and H_p/H_1 per trial. The horizontal segments associated with a given subject indicate the right leg (thin line) and left leg (thick line) overall mean values for that subject, corresponding to the coordinates of a point in Fig. 2*A*. Each trial's average right and left leg H_p/H_1 are indicated by empty and filled circles, respectively. The pairs of points that are not statistically different are indicated by an arrow. The population right and left leg means of H_p/H_1 (diamonds) are shown in the last column, the values being equivalent to the mean plateau levels in Fig. 1. SE is indicated for each point by a vertical bar (not visible when the value is too low).

than the left in the first trial, whereas in the second trial, which happened less than a minute later, the left leg had a higher plateau level than the right, both statistically significant (paired *t*-test, $P < 0.05$). Such a side switching was found again, in a statistically significant level, in *subject S8,* while all the others showed consistency between trials, i.e., showed no side switchings. The data points in Fig. 2*D,* when analyzed with more detail for each subject, showed that five subjects had, at least in one trial, a significantly larger H_2/H_1 value for the right leg, two for the left leg, and three showed no statistically significant asymmetry.

Summarizing the results so far, from a population analysis, there were no differences between right and left leg H-reflex parameters using the simultaneous train of stimuli paradigm. When data from individual subjects were tested, there was a tendency for less depression in the mean H-reflex amplitude for the right leg in 7 of 10 subjects (even though in 2 of the 7 subjects, 2 consecutive trials showed opposite directions in the asymmetry). Therefore despite the probably low power of the *t*-test applied to detect asymmetries in our population data, it is clear that individuals with right side dominance can show more depressed reflexes on either side (Fig. 2*A*). Additionally, in the same subject and within a minute, there may be a switching of the side where the reflex depression is higher (Fig. 3).

Auto-covariance analysis

For the auto- and cross-covariance analyses, each H-reflex sequence with 500 responses per leg had its first 10 responses discarded to eliminate the depression transient. The remaining 490 responses were detrended by subtraction of the best straight line fit to the time series. Failure to detrend may cause considerable artifacts in covariance and spectral analyses. Examples from two subjects are shown in Figs. 4 and 5, where the sequences are displaced vertically for easier visualization, the right leg values being shown above those from the left leg. Figure 4, *A* and *B,* suggests that there is a tendency for rather fast variability around the baselines (i.e., relatively narrow auto-covariance peak, see Fig. 6*B*). Figure 4*B* suggests a tendency for positive (negative) peaks in the right leg to correspond to positive (negative) peaks at the left leg (nonzero peak at 0 lag in the cross-covariance, see Fig. 6*D*). Figure 5 suggests that both legs have some tendency for slower variations around the baseline (wider peaked auto-covariances than those for Fig. 4, see Fig. 6*B*) and fewer coincidences of equal signed peaks

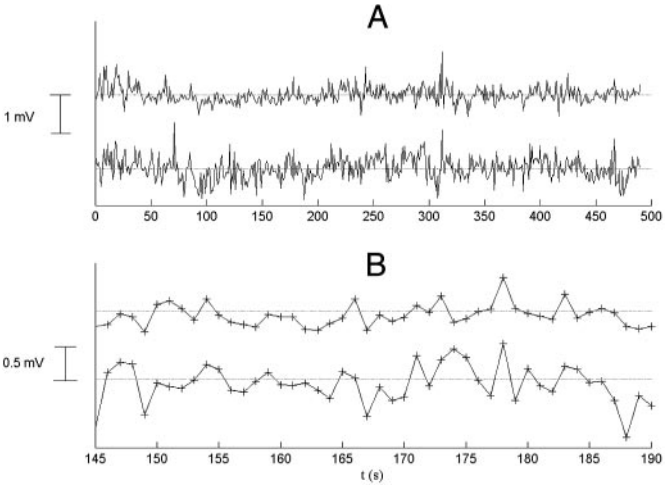

FIG. 4. Long sequences of H-reflex amplitudes from a subject's (*S4*) right (*top*) and left (*bottom*) legs to 1-Hz trains of stimuli, after detrending. The horizontal lines indicate the corresponding reference baselines. *A*: all the 490 reflex amplitudes from each leg. *B*: the reflex amplitudes from responses 145 to 190. These data are an example of sequences with narrow auto-covariance peaks (memories 6 and 8 for right and left legs, respectively; see ahead for definition of auto-covariance memory). They were used to compute the nonflat cross-covariance shown in Fig. 6*D*.

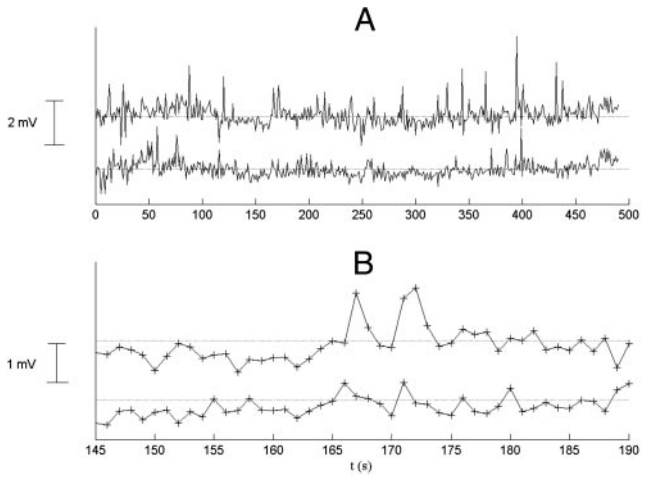

FIG. 5. Long sequences of H-reflex amplitudes from a subject's (*S5*) right (*top*) and left (*bottom*) legs that yield a flat cross-covariance. The horizontal lines indicate the corresponding reference baselines. *A*: all the 490 reflex amplitudes from each leg. *B*: the reflex amplitudes from responses 145 to 190. These data yield auto-covariance memories equal to 10 and 35 (see ahead for definition of auto-covariance memory) for right and left legs, respectively, and a flat cross-covariance.

between both leg sequences (very small or no peak at 0 lag in the cross-covariance).

A quantification of the features of H-reflex amplitude sequences, such as those shown in Figs. 4 and 5, was achieved by the unbiased auto- and cross-covariance sequences. Each auto-covariance sequence was normalized by the variance of the corresponding H-reflex amplitude sequence so that the maximum auto-covariance value was equal to 1 (at lag 0). To test for the whiteness of the series, i.e., that each H-reflex amplitude is not correlated with any other in the sequence, we checked if all the auto-covariance samples, except for the central one at lag 0, were within the 95% confidence interval given by $\pm 1.96/\sqrt{N}$, where N is the number of samples in the H-reflex sequence (in our case $N = 490$) (Brockwell and Davis 1991).

In the overall, 15 sequences out of 48 H-reflex amplitude sequences (each with 490 responses, from both legs of 10 subjects), including right and left legs indistinctly, could be considered white sequences (e.g., Fig. 6*A*) and the rest non-white sequences. In physiological terms, the 15 white sequences would mean that there is no linear correlation between the amplitudes of adjacent H-reflexes in the train of depressed reflexes elicited at every 1 s. In a looser sense, this may mean that each H-reflex amplitude is independent of the amplitude of any other H-reflex in the train. Of the 33 nonwhite H-reflex trains, there were auto-covariances with narrow or wide peaks, as exemplified for two subjects in Fig. 6*B*. Their detrended H-reflex amplitude sequences would be somewhat similar to the examples for right leg in Fig. 4 and left leg in Fig. 5, respectively. When the complete set of 48 sequences was reduced to a set containing only 32 very stationary H-reflex amplitude sequences (16 pairs from 7 subjects), the results showed that 10 of the 32 were white, the same proportion as that found for the complete set. The memory associated with an H-reflex train was defined as the positive lag where the auto-covariance first crossed the upper level of the confidence interval when decreasing from value 1 at lag 0 (for example, in Fig. 6*B* the memory for the wider peaked auto-covariance would result about 24 s and for the narrower 6 s). The measured memory values ranged from 2 to 50 s. In the reduced set (32 H-reflex amplitude sequences), when a subject's right leg had a white H-reflex amplitude sequence, so did his left leg. Same day replication (in 2 subjects of the 7) did not change the

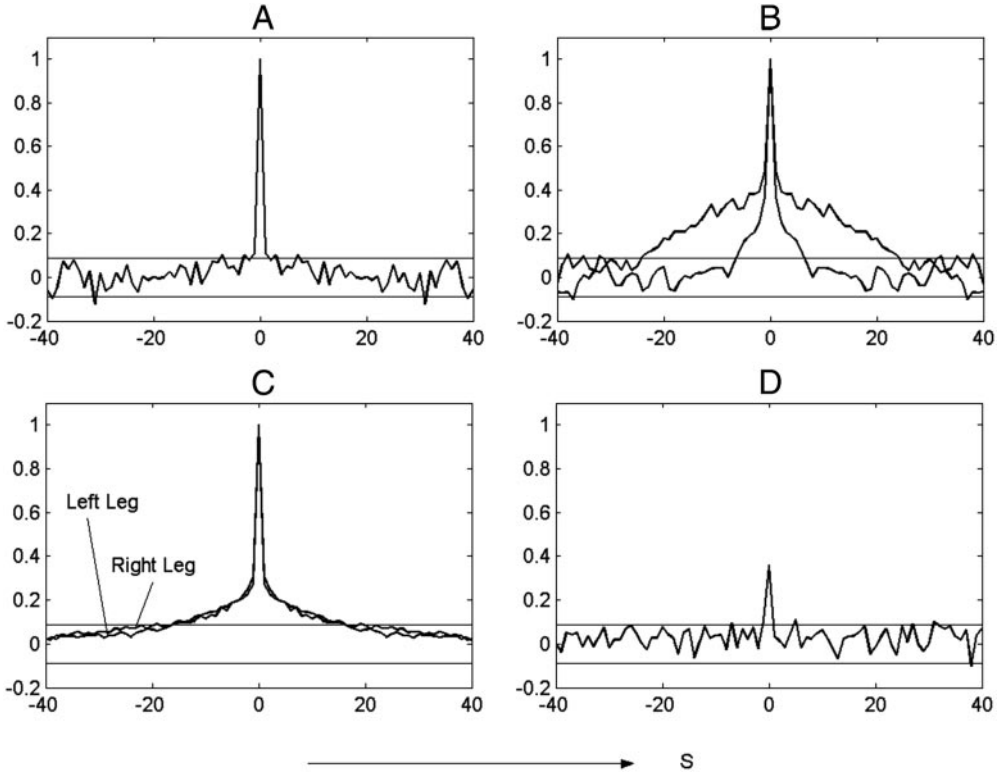

FIG. 6. Auto- and cross-covariances computed from sequences of 490 H-reflex amplitude sequences. The band delimited by the 2 horizontal lines indicates the 95% confidence interval. *A*: auto-covariance sequence of the right leg of *S3*. Because practically all the samples at lags $\neq 0$ fell within the confidence interval, this exemplifies a white H-reflex amplitude sequence. *B*: auto-covariance sequences from 2 subjects: the 1 with the wide peak (crossing the upper boundary of the confidence band at -24 s and 24 s) comes from *subject S7* (left leg) and the other (peak crossing the upper boundary of the confidence band at -6 s and 6 s) comes from *subject S9* (right leg). Both examples correspond to non-white H-reflex amplitude sequences. *C*: mean auto-covariance sequences computed separately from all the subject's right legs and left legs (the 2 curves are almost superposable). *D*: cross-covariance between the right and left leg (whitened) H-reflex amplitude sequences of *subject S4*. A clear peak at lag 0 is seen above the confidence band.

general auto-covariance type, if white, it remained white, if nonwhite, it remained nonwhite (except for 1 subject that had a white transformed into a nonwhite auto-covariance in the replication). The memory values found for the 11 pairs of nonwhite sequences for the right and left legs were (8, 10), (6, 8), (10, 35), (10, 6), (5, 24), (3, 13), (12, 2), (6, 20), (50, 37), (15, 27), and (32, 30) seconds. It is noteworthy that in some cases the variability in one leg had quite different memory value than in the other. One subject who had the experiment repeated in different days showed in both days white H-reflex amplitude sequences in both legs. The other subject showed wide-peaked auto-covariances (mean memory 37 s) in both days but in one same day replication there was a change to narrow peaked auto-covariance in both legs (memory around 9 s).

An overall average of auto-covariances separating right leg from left leg resulted in very similar auto-covariance sequences for both legs, exhibiting a peak with a width around 32 s (Fig. 6*C*), which means an average memory value for H-reflex trains around 16 s.

Cross-covariance analysis

The cross-covariance sequence (normalized to give value 1 for fully correlated trains) was tested for correlation between the sequences of H-reflexes obtained from both legs simultaneously following the procedure described by Brockwell and Davis (1991). As the cross-covariance estimated from raw experimental sequences may indicate correlation even when the two series are independent, each sequence was whitened by inverse filtering before computing the cross-covariance. This was achieved by adjusting an auto-regressive (AR) model to each sequence of H-reflexes and then filtering each sequence by its corresponding inverse filter obtained from the AR coefficients. The order of each AR model was chosen (in the range from 1 to 20) to minimize the AIC criterion (Brockwell and Davis 1991). Under this condition of whitened simultaneous sequences, the 95% confidence interval for the cross-covariance was determined as $\pm 1.96/\sqrt{N}$. Cross-covariance samples out of the confidence interval would suggest a correlation between the two series at the corresponding lags. If no samples are out of the confidence interval, then one may suppose the two series are independent (or more strictly, uncorrelated).

For this analysis, only the reduced set of 16 pairs of H-reflex amplitude sequences was used. Eight pairs of the 16 had flat cross-covariance sequences (i.e., samples fell within the confidence interval), meaning the H-reflex amplitude sequence from one leg was uncorrelated with the other leg's sequence. The other eight pairs showed a statistically significant cross-covariance peak at lag 0. The peak amplitudes ranged from 0.17 to 0.36 (i.e., well above the confidence interval upper boundary of 0.0885). An example from one of the subjects is seen in Fig. 6*D*, corresponding to the H-reflex amplitude sequence shown in Fig. 4. This finding indicates that H-reflex amplitude variations tend to fluctuate synchronously in both legs. Of seven same-day replications, the cross-covariances remained flat in two cases, changed from flat to nonflat in three cases, and remained nonflat in two cases. The first subject that had the experiment repeated in a different day had flat cross-covariances in both days, and the second subject changed from a nonflat to a flat cross-covariance on the second day of experiment.

DISCUSSION

An important approach in this research was the *simultaneous* recording of H-reflexes from both legs instead of recording first one leg's responses and afterward the other's. In the latter situation, any change in the subjects' state (Schieppati 1987) between the times of the recordings from each leg could introduce considerable differences in reflex sizes (mean and amplitude variations) in the two legs.

Preliminary experiments

The initial experiments were performed to determine the existence of any influence of a posterior tibial nerve stimulation on the contralateral soleus Ia-terminal-motoneuron pool. These contralateral influences could arise from muscle Ia, Ib, and II afferents (Aggelopoulos and Edgley 1995; Aggelopoulos et al. 1996; Baxendale and Rosenberg 1976, 1977) and also from cutaneous afferents (Koceja and Kamen 1992; Robinson et al. 1979; Rosenberg 1970). Because in our experiments the stimuli were somewhat small (to obtain H-reflex amplitude of $0.2 \times M_{max}$), group II muscle afferents were probably not activated (Marque et al. 1996). Afferent fibers of cutaneous origin acting across at least two synapses have been described as having stronger contralateral effects than muscle afferents (Koceja and Kamen 1992; Robinson et al. 1979). In spite of all these possibilities of contralateral effects, our results showed no significant difference between control and H responses conditioned by either a single contralateral stimulus (as also found by Nozaki et al. 1996) or by a contralateral train of stimuli over the tibial nerve that ended 1 s before the test stimulus. The latter result excluded a hypothetical long loop effect potentiated by a summation of effects due to the train of stimuli. The conclusion from the preliminary experiments was that simultaneous trains of stimuli applied to both legs permit an independent and simultaneous analysis of the reflex systems of the two legs.

Asymmetries of parameters obtained from bilateral H-reflexes

In the present work, no statistically significant asymmetries were found in the mean plateau level, coefficient of variation and time constant of trains of H-reflex amplitudes between right and left legs in a population of 10 subjects (Fig. 2, *A–C*). All our subjects were absolutely positive as to their right-handedness and their "right-footedness." Therefore in our population sample, lateral dominance does not seem to affect depressed H-reflex parameters such as mean amplitude and level of variability when seen from a population viewpoint.

The data from this research also showed that there is a significant positive correlation between right and left leg parameter values, e.g., if a given subject has a strong H-reflex depression on its right leg then its left leg will also exhibit, with high probability, a strong depression.

Looking at the individual data from each subject, we observed significant differences in H_p/H_1 between the two legs in all of the 10 subjects tested, indicating an asymmetry in the degree of H-reflex depression in each subject (Fig. 3). Never-

theless, in spite of all being right handed, seven subjects showed larger (less depressed) responses for the right leg and three for the left leg. Additionally, it is interesting to note that from one trial to another (less than 1 min apart) the same subject could switch from a left to a right leg asymmetry (2 cases in 10).

As no significant difference was found for the decay time constants in the two leg H-reflex trains (Figs. 1 and 2*C*), it seems that the mechanisms responsible for H response depression act with similar dynamics on the soleus motoneuron pools of both legs. As the mechanism behind H-reflex depression seems associated with the presynaptic terminal (Hultborn et al. 1996; Kohn et al. 1997), this would suggest that the Ia terminals on both sides have similar dynamic behavior in terms of neurotransmitter release.

Asymmetries in soleus muscle H-reflex RCs in normal subjects have been described in the literature (Chandran et al. 1988; Goode et al. 1980; Nativ et al. 1989; Tan 1985a,b). Our data comparing H_2/H_1 (Fig. 2*D*), corresponding to a single point of the RC (at an inter-stimulus interval of 1 s), showed no significant asymmetry in the population, similarly to the findings of Aymard et al. (2000) for a 2-s interval between the two stimuli.

In the literature, the reports have been somewhat contradictory with respect to the correlation of asymmetries in the RC obtained from both legs and the dominant side (Chandran et al. 1988; Goode et al. 1980; Nativ et al. 1989; Tan 1985a,b). Our results, based on H_2/H_1 or H_p/H_1, indicated that right-footed subjects may have an asymmetry either to the right or to the left, which is potentially labile in a few subjects (Fig. 3), a result remindful of that for H_2/H_1 presented by Chandran et al. (1988).

In short, the statistical tests did not reject the hypothesis that the means, CVs, and time constants of H-reflex amplitudes in a train were equal for both legs in our population of subjects. Perhaps more importantly, the experiments showed that each subject had a significant asymmetry that was not related to side dominance and that the asymmetry could even switch sides in a few minutes. Probably lateral dominance is less important in the leg than in the arm, and hence, its effects may appear in a more restricted number of parameters and with less intensity in electrophysiological measurements.

Within the context of analyzing a new data point with respect to the data points obtained in this research (e.g., Fig. 2*A*), one could use the Mahalanobis distance (Mardia et al. 1979) to define how much the new point is different from the available cluster of reference points, which may be described approximately by a bivariate normal distribution. All points on the 95% probability ellipse are at a Mahalanobis distance $\sqrt{5.99} = 2.4472$ from the mean of the bivariate distribution, all other points inside the ellipse being at a smaller distance. Given a new data point, e.g., from a neurologic patient, if its Mahalanobis distance to the center point of the ellipse is larger (smaller) than 2.4472, then it could be considered different from (similar to) the control case. The value of this distance could be relevant in characterizing the degree of dysfunction.

Auto-covariance and cross-covariance analyses

The mean auto-covariances from both legs in the population of subjects matched extremely well (Fig. 6*C*), suggesting that whatever processes cause H-reflex variabilities, their time structure is similar for both legs on average.

However, the different types of auto-covariances and the individual bilateral differences that were obtained in our experiments may raise a few questions: why did some subjects present white sequences of H-reflex amplitudes while others showed considerable memory between subsequent H-reflexes? Why did some subjects have quite similar memory values in both legs while others did not? What are the sources of these variabilities and what do they depend on?

The correlations found between the amplitudes of two H-reflexes elicited 1 s or more apart in response to a train of stimuli applied to the same leg may arise from both intrinsic and extrinsic sources to the motoneuron-Ia synapse system. Intrinsic properties (like calcium-dependent potassium conductance and homosynaptic depression, for example) are probably unable to account for the long memories associated with many of the computed auto-covariances. Research in cats has suggested that indeed extrinsic factors—modulations of Ia presynaptic inhibition and of motoneuronal synaptic inputs—are the main causes of reflex amplitude variability (Gossard et al. 1994; Rall and Hunt 1956; Rudomin et al. 1969; Somjen and Heath 1966). Both modulations may come from the periphery and from upper centers, but the former may probably contribute little in our experiments because the subjects were sitting in a very relaxed state. The corticospinal and reticulospinal descending pathways are perhaps the most probable agents causing the slow modulations in reflex responses. The data from our work showed a good symmetry between CV values from both legs and very similar regression lines relating CV and mean plateau level. These results suggest that there is a balanced distribution of synaptic activation on the motor neuron pools and Ia-terminals associated with the soleus muscles of both legs.

The auto-covariance sequences we report in RESULTS may give some indication on possible differences in inputs to the Ia-motoneuron system between the white and nonwhite cases. If we assume that each motoneuron (or presynaptic inhibition interneuron on a Ia terminal) receives an independent input, the reflex variability may have a white characteristic if all inputs are white or have a memory smaller than 1 s (the interval between consecutive reflexes in the H-reflex trains). Otherwise, the reflex variability will have a memory that is some average of each input's memory. Conversely, if the inputs are correlated, the resulting reflex variability may be white only if the cross-covariances between pairs of inputs and the auto-covariances of each input have a memory smaller than 1 s. If either the cross-covariances or individual auto-covariances of the inputs have longer memory, the reflex sequence will be nonwhite. These theoretical considerations, based on our data and on the theory of time series analysis, are an expansion of hypotheses put forward by other researchers (Gossard et al. 1994; Rall and Hunt 1956; Rudomin and Dutton 1969; Rudomin et al. 1969) who used cat data. Summarizing, we suggest that a white reflex sequence would be more probable to occur with a predominance of independent inputs, while a nonwhite reflex sequence may be generated by either independent nonwhite sources or correlated sources (white or nonwhite). An interesting point is that H-reflex trains could result with long memories (i.e., auto-covariances with wide peaks) arising from fluctuations of excitability that are independent

from one motoneuron (or Ia terminal) to another. The important requirement in this case is that the fluctuations have to be nonwhite with a spectrum that has more power in the low frequencies. For example, sequences with approximately $1/f$ spectra (which are nonwhite and have a long memory) may arise from a weighted superposition of a large number of *independent* low-pass or band-pass random sequences (Wornell 1996). On the other hand, the cross-covariances we found with a statistically significant peak at zero lag necessarily imply some degree of correlation between the inputs to the homonymous motoneuron pools associated with the two legs. Nozaki et al. (1996) suggested that slow fluctuations in the H-reflex amplitudes were synchronized in the two legs due to the activity of supraspinal centers. Common bilateral inputs to lumbo-sacral motoneurons, as originating from pontomedullary reticulospinal axons (Matsuyama et al. 1999), could certainly be contributing to such a correlation.

Data from six normal subjects reported in Nozaki et al. (1995, 1996) had power spectra of trains of H-reflex amplitudes (elicited every 1 s) with a $1/f^{\beta}$ behavior ($\beta = 0.75 \pm 0.26$) and a relatively strong time correlation. Indeed, some of our auto-covariances (e.g., Fig. 6*B*) are typical of "long memory processes" (Brockwell and Davis 1991), which could be associated with $1/f$-type fractal random processes. This finding occurred in about a third of our auto-covariances. However, on the opposite extreme, another third of the cases exhibited white-noise-like auto-covariance sequences, i.e., zero-memory processes, or equivalently, flat power spectra. Finally, another third of the cases showed rather short memory sequences of H-reflexes. Therefore our data extended considerably the reports by Nozaki et al. (1995, 1996) and raise questions on the physiological meanings of, and the mechanisms behind, the different types of auto-covariances we found.

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