

Backward and Forward Walking Use Different Patterns of Phase-Dependent Modulation of Cutaneous Reflexes in Humans

J. DUYSSENS, A. A. M. TAX, L. MURRER, AND V. DIETZ

Department of Medicine, Physics, and Biophysics, University of Nijmegen, 6500 HB Nijmegen; Department of Clinical Physics, University of Rotterdam, 3075 EA Rotterdam, The Netherlands; and Paraplegic Centre, University Hospital Balgrist, 8008 Zurich, Switzerland

SUMMARY AND CONCLUSIONS

1. The phase-dependent modulation of medium-latency (P2) (70–80 ms) responses in semitendinosus (ST), biceps femoris (BF), rectus femoris (RF), and tibialis anterior (TA) was studied with the use of low-intensity stimulation (2 times perception threshold) of the sural nerve. The shocks were given in a random order at 16 phases of the step cycle in 10 normal subjects during forward walking (FW) or backward walking (BW) on a treadmill.

2. All subjects exhibited P2 responses in all muscles studied both during BW and FW. The amplitude of the facilitatory P2 responses showed phase-dependent changes that could not have been predicted on the basis of the variations in background activity throughout the step cycle.

3. During FW, the P2 facilitatory responses in BF were large (with respect to the background activity) throughout the whole step cycle except for a short period near the end of the swing phase. In ST the responses were smaller and appeared primarily at the end of the stance phase and during the first part of the swing phase. During the second half of swing the P2 responses were basically suppressive. A modulation pattern similar to the one in ST was found in RF and TA, except that there was no reversal to suppressive responses in the swing phase in RF. Instead, a reduction in the amplitude of the facilitatory P2 responses occurred.

4. During BW, the modulation pattern recorded in the same subjects was different from the one seen during FW. Large facilitatory P2 responses were present in all muscles in middle and late swing. In the first half of stance the responses were most prominently seen in BF and RF. At the end of stance and/or at the onset of swing the facilitatory responses decreased in amplitude (BF and RF) or reversed to P2 suppressions (ST and TA).

5. We conclude that there are both facilitatory and suppressive pathways from the sural nerve to the leg muscles studied and that the balance of activity in these paths is phase dependent during both FW and BW. It is suggested that the phase-dependent modulation of P2 responses could largely rely on a central motor program. During BW the same motor program is used as during FW, but possibly running in reverse, thereby causing a shift both in the timing of the reflex reversal and in the periods of reflex suppression.

INTRODUCTION

The amplitude of reflex responses with medium latency (P2 responses) elicited by stimulation of cutaneous afferents from the foot depends on the phase of stimulation within the step cycle, both in the intact cat (Abraham et al. 1985; Duysens and Loeb 1980; Duysens and Stein 1978; Forssberg 1979; Pratt et al. 1991) and in humans (Belanger and Patla 1987; Crenna and Frigo 1987). This “phase-dependent modulation” is expressed in its most extreme form in reflex

reversals. For example, stimulation of the posterior tibial nerve in humans elicits P2 responses in flexors during early swing, but the same stimulation yields P2 extensor responses during early stance (Duysens et al. 1990). A second type of reversal consists of a transition from facilitatory P2 responses in ankle flexors during early swing to suppressive P2 responses in late swing (tibialis anterior, TA; Duysens et al. 1990; Yang and Stein 1990).

In humans, little is known about the mechanisms underlying such reflex reversals. In the cat, however, it seems that part of the phase-dependent modulation is due to the intervention of a central motor program for locomotion, referred to as a central pattern generator (CPG). Rhythmic alternating activity in flexor and extensor muscles persists in paralyzed cats (fictive locomotion). Despite the absence of rhythmic afferent input in such preparations, a phase-dependent modulation of cutaneously evoked responses is present and it shows similarities with the modulation patterns seen in the intact animal (Andersson et al. 1978; LaBella et al. 1992; Schmidt et al. 1989; Schomburg and Behrends 1978a,b). On the other hand, it has been demonstrated in the cat that afferent input can also be important in modulating reflex transmission. Depending on whether the limb is held in a flexed or extended position, the response to distal cutaneous stimulation may appear either in extensors or flexors, respectively (Baxendale and Ferrell 1981; Grillner and Rossignol 1978a; Rossignol and Gauthier 1980).

The present experiments on responses to sural nerve stimulation during both backward walking (BW) and forward walking (FW) were designed to shed some light on the mechanisms controlling phase-dependent modulation of cutaneously evoked responses in the human and to test whether FW and BW could have a common neural substrate. Both for the crayfish and for the cat it was proposed that the same neural mechanism (“motor program”) is used for both FW and BW (for review see Clarac 1984; Pearson 1993). Detailed studies on BW in the cat (Buford and Smith 1990, 1993; Perell et al. 1993) indicated that FW and BW are both controlled by the same pattern generator, without the need to reorganize connections between joint units (Grillner 1981).

In humans, the “program reversal” idea for bipedal BW was tested by studying the kinematics, biomechanics, and electromyogram (EMG) patterns during both FW and BW (Thorstensson 1986; Vilensky et al. 1987; Winter et al. 1989). The leg trajectories and the EMG timing of hip muscles during BW were similar to those of “reversed-in-time”

FW. The biomechanical analysis of Winter et al. (1989) suggested that "backward walking is almost a simple reversal of forward walking."

The question of a reversed motor program has important implications with respect to the pattern of phase-dependent modulation. On the basis of animal experiments (LaBella et al. 1992) it is reasonable to assume that the phase dependency of cutaneous reflex responses depends at least partly on the action of the motor program generated by the spinal CPG for locomotion. If this program is reversed (for example, by walking backward), one might expect to see that the pattern of phase-dependent modulation changes as well. In the cat this question was investigated by Buford and Smith (1993), who found no dramatic changes in the modulation pattern during BW compared with FW, except those expected on the basis of the differences in muscle activation related to the two forms of locomotion. However, these authors sampled only during a few phases of the step cycle and it is possible that subtle changes were not observed because of this limitation.

Another possibility is that the reversal is linked to touch-down. It has indeed been suggested that the reversal from facilitatory to suppressive responses in TA may be related to the need to avoid additional ankle flexion in the crucial period around footfall (Duysens et al. 1992b; Stein 1992). If this functional interpretation is correct, one would expect that such reversal would occur in equivalent phases during BW, although in the latter case the landing is slightly different (toe strike instead of heel strike).

Afferent input, especially related to hip position (Grillner and Rossignol 1978b), may also play a role. For example, suppose that the TA reversal is related to the hip reaching a given position at end swing during FW; then during BW the equivalent reversal should occur near the transition from stance to swing (because the hip is flexing during stance rather than during swing).

These different hypotheses were tested on responses in four muscles that were chosen for the present study on BW because their responses are already well documented through previous studies on FW or running (Duysens et al. 1990, 1991, 1992b, 1993; Tax et al. 1995; Yang and Stein 1990). In the present study the subjects were tested for their responses during both FW and BW to allow a direct comparison. In addition, the hamstring muscles semitendinosus (ST) and biceps femoris (BF) have a special significance in various CPG models used to predict the motor pattern of BW (Perret and Cabelguen 1980; Smith 1986).

Preliminary communications have been published in abstract form (Murrer et al. 1994).

METHODS

Experimental setup

A detailed description of the methods used can be found in previous publications from our group (Duysens et al. 1990, 1991, 1992b, 1993; Tax et al. 1995). The data presented in the present paper came from experiments performed on a group of 10 normal (9 male, 1 female) subjects aged between 21 and 45 yr, tested for both FW and BW. The experiments were carried out in two laboratories (Department of Clinical Neurophysiology in Freiburg and Department of Medical Physics and Biophysics in Nijmegen).

The experiments were conducted in conformity with the declaration of Helsinki for experiments on humans. All subjects had given informed consent and had no known history of neurological or motor disorder. The subjects were asked to walk on a treadmill at 4 km/h either in the forward or backward direction while wearing a safety harness that was fastened to the ceiling.

The setups in the two laboratories involved were completely comparable except for the detection of foot contact with the treadmill. In the Freiburg laboratory this information was provided for by two built-in force plates, corresponding to the split-belt configuration of the treadmill. In Nijmegen very thin insole foot switch systems (designed in collaboration with Algra Fotometaal, Wormerveer, The Netherlands) were used. Comparative testing in Freiburg proved that both systems yielded similar results for the timing of stance and swing in bipedal locomotion.

EMG activity was recorded in both legs by means of pairs of surface electrodes over the ST, BF, rectus femoris (RF), and TA. BF and ST are knee flexors and hip extensors, RF is a knee extensor and a hip flexor, and TA produces dorsiflexion at the ankle. The stimulation electrodes were positioned on the left leg near the middle of the distance between the external malleolus and the Achilles tendon, where the sural nerve is closest to the skin surface. The electrical stimulus consisted of five rectangular pulses 1 ms in duration given over a period of 21 ms. A custom-made constant-voltage stimulator provided the desired stimulus amplitude.

Experimental protocol

The FW experiment was always performed first, directly followed by the BW experiment. The FW and BW data were sampled in a period of typically 2 h. An experiment started with several short periods of walking on the treadmill. In these periods the subject was trained to walk at a comfortable, constant pace. Between these periods, during quiet standing, the perception threshold (PT) was determined psychophysically by gradually increasing (to above PT) and decreasing (to below PT) the stimulus amplitude in at least three series. In general, the PT appeared to decrease during the first half hour, presumably because the stimulation electrodes, firmly pressed over the nerve with elastic straps, gradually settled within the cutaneous tissue. The attainment of a constant PT was an indication for stable stimulation conditions and therefore a prerequisite for starting the experiment. All subjects reached a stable PT (23 ± 4 V, mean \pm SD) within 30–60 min. No data were sampled in this period.

In the FW and BW experiments, the stimuli were varied with respect to the timing of presentation in the step cycle. Ipsilateral and contralateral footfall served as reference points for the first and second half of the step cycle, respectively. This enabled a reproducible stimulation at 16 equidistantly distributed phases in the step cycle. Stimulus intensity was kept constant at 2 PT.

Every stimulus condition ($N = 16$) was presented 10 times. For every stimulus trial (total $N = 160$) a corresponding sample without stimulation was taken. All 320 trials occurred in random order. The successive stimulus presentations were separated by a random interval in the range of 2–5 s, which corresponds to at least two cycles of unperturbed walking. Thus a typical experimental run lasted for ~30 min.

At the end of each experiment the PT was determined once more. In general, it was only slightly lower compared with the threshold measured before the walking experiment (~8% during FW and 3% during BW), indicating stable stimulation conditions. The latter was confirmed by also checking the stability of the threshold for full irradiation of evoked sensation to the lateral side of the foot (constant at ~2 times the initial PT just before the main experiment).

Data sampling

The EMG signals were preamplified (by a factor of 10) close to the subject to minimize signal distortion during data transfer. After further amplification they were high-pass filtered (cutoff frequency 3 Hz) to avoid slow signal drifting. Then, the signals were full-wave rectified and low-pass filtered (cutoff frequency 300 Hz). A simple sample-and-hold circuit allowed the amplitude of the transient current signals of the (constant voltage) stimulus to be measured.

The EMG envelopes, the stimulus voltage and current, the ipsilateral and contralateral foot switch signals (or ground contact forces), and a digital code referring to the stimulus condition were A-D converted (500 Hz) and stored on disk. The storing of each trial started 100 ms before stimulation and lasted for 1,600 ms.

Theoretically, the sample rate of 500 Hz is rather low compared with the cutoff frequency of 300 Hz used for low-pass filtering the EMG signals. In practice this sample rate appeared to be sufficiently high. Increasing the sample rate to 1,000 Hz did not lead to appreciable improvement of the signals for the purpose of this study. Thus the information content in the higher-frequency range of the EMG signals was considered to be negligible.

Data analysis

Stability of the stimulation conditions was a primary concern for the present study. Instability could in principle arise from two sources. First, irregularity of the gait could cause the preprogrammed stimulus timing to become inappropriate. For all subjects, the cadence during 4-km/h walking appeared to be very stable. The standard deviation of the step cycle time was typically <30 ms (3%), which was rather small compared with the average time interval of 67 ms between the 16 adjacent step cycle phases. Second, the movements during gait could have caused variations in the transfer impedance of the stimulus electrode configuration and as a consequence could have resulted in deviations of the applied currents (because constant-voltage stimulation was used). The current variations were measured for each experiment.

All current values were first individually normalized with respect to the mean stimulation current taken over the total step cycle, thus allowing intersubject comparison. The current was the maximum measured in a window between the onset of stimulation and the following 50 ms. The mean values at any given phase never deviated by >3% from the mean across all phases. Thus the applied current was basically constant throughout the step cycle during FW and BW. Population averaging yielded a current level of 8.3 ± 1.9 (SD) mA and 9.5 ± 2.4 (SD) mA for FW and BW, respectively, for the stimulus intensity (2 PT) used. It may be argued that even for constant currents one cannot be sure that the current to the nerve stays constant. Some authors have controlled for the constancy of stimulation by using mixed nerve stimulation and monitoring of the M waves (Yang and Stein 1990). So far all our previous results on reflex modulation, with the use of mixed nerve stimulation (tibial nerve; Duysens et al. 1990, 1991, 1992b, 1993), have been completely compatible with the results obtained by other authors using the M wave control method. The latter method cannot be applied to pure cutaneous nerves.

The EMG analysis started with a procedure for the detection of reflex responses. First, the 10 different trials of each stimulus condition were averaged. This resulted in an averaged "reflex" trial for each stimulus phase. An equal number of averaged "control" trials without stimulation were taken at the equivalent phases. To obtain the "pure" reflex responses the averaged control trials were subtracted from the corresponding reflex trials.

The subtraction technique allowed measurement of both facilitatory and suppressive responses. The latency of these responses was defined as the onset of the positive and negative deviations,

respectively, from the zero line. The time window for the reflexes was set by visual inspection (time resolution 2 ms) taking the following criteria into account.

1) The windows were set around the earliest reflex responses that appeared most consistently over the muscles and the subjects. These were the so-called "middle"-latency reflexes (Yang and Stein 1990), or P2 responses (Duysens et al. 1993) that occurred roughly 70–80 ms after stimulation and typically lasted for ~30 ms.

2) One single optimal window was set for all 16 stimulus phases (Duysens et al. 1991).

3) When a muscle showed little or no responses no adequate window could be set, yet an equivalent response measure was required to calculate population averages. In that case an extrapolated window was used, calculated from the time windows determined for (in order of priority) the same muscle at another gait, other nearby muscles in the same leg, or the same muscles in other subjects (Tax et al. 1995).

For the averaged reflex, control, and the corresponding subtracted trials the mean EMG values within the window were calculated. The resulting data underwent both an amplitude and a time normalization procedure in order to enable a proper intersubject comparison. For the amplitude normalization the EMG data were scaled for each muscle to the maximum control value in the step cycle (i.e., the maximum spontaneous activity during 4-km/h FW or BW).

For the normalization of the time axis the step cycle was subdivided into 16 equal intervals (on average 71 ms for FW and 62 ms for BW). The responses will be presented according to their appearance in 1 of the 16 intervals. The statistical significance of the responses was tested by comparing the amplitude of the unsubtracted reflex peak of each stimulation trial with the amplitude of a matched control sample peak with the use of a Wilcoxon matched-pairs signed-rank test (significance at $P \leq 5\%$).

RESULTS

Population averaging yielded a total step cycle time of $1,130 \pm 85$ (SD) ms and 999 ± 70 (SD) ms and a stance duration of 680 ± 52 (SD) ms and 583 ± 27 (SD) ms for FW and BW, respectively. Thus there was a tendency toward shorter step cycle duration (decrease of 13%) in BW. The relative duration of the stance phase was about equal in FW and BW ($60 \pm 3\%$, mean \pm SD, for FW and $59 \pm 4\%$, mean \pm SD, for BW). These stride characteristics are in quite good agreement with earlier experimental data (e.g., Kramer and Reid 1981; Thorstensson 1986).

At 1 of 16 phases of the step cycle a stimulus train was applied over the sural nerve at 2 PT both during FW and BW. An example of a typical averaged ($N = 10$) EMG response in ST is seen in Fig. 1, *inset*.

P2 responses have a latency between 70 and 80 ms. Earlier responses were occasionally observed as well but they were inconsistent or very small. This paper therefore is devoted entirely to the larger reliable P2 responses that were observed in all 10 subjects investigated.

To obtain responses such as those shown in Fig. 1, the background EMG activity was subtracted ("subtracted" responses, see METHODS). This allowed study of both facilitatory and suppressive responses. The responses were measured as the mean activity within windows, which were set as shown in Table 1. Note that there were only minor differences in latency between the various muscles.

The measurements of P2 responses in ST at 16 different

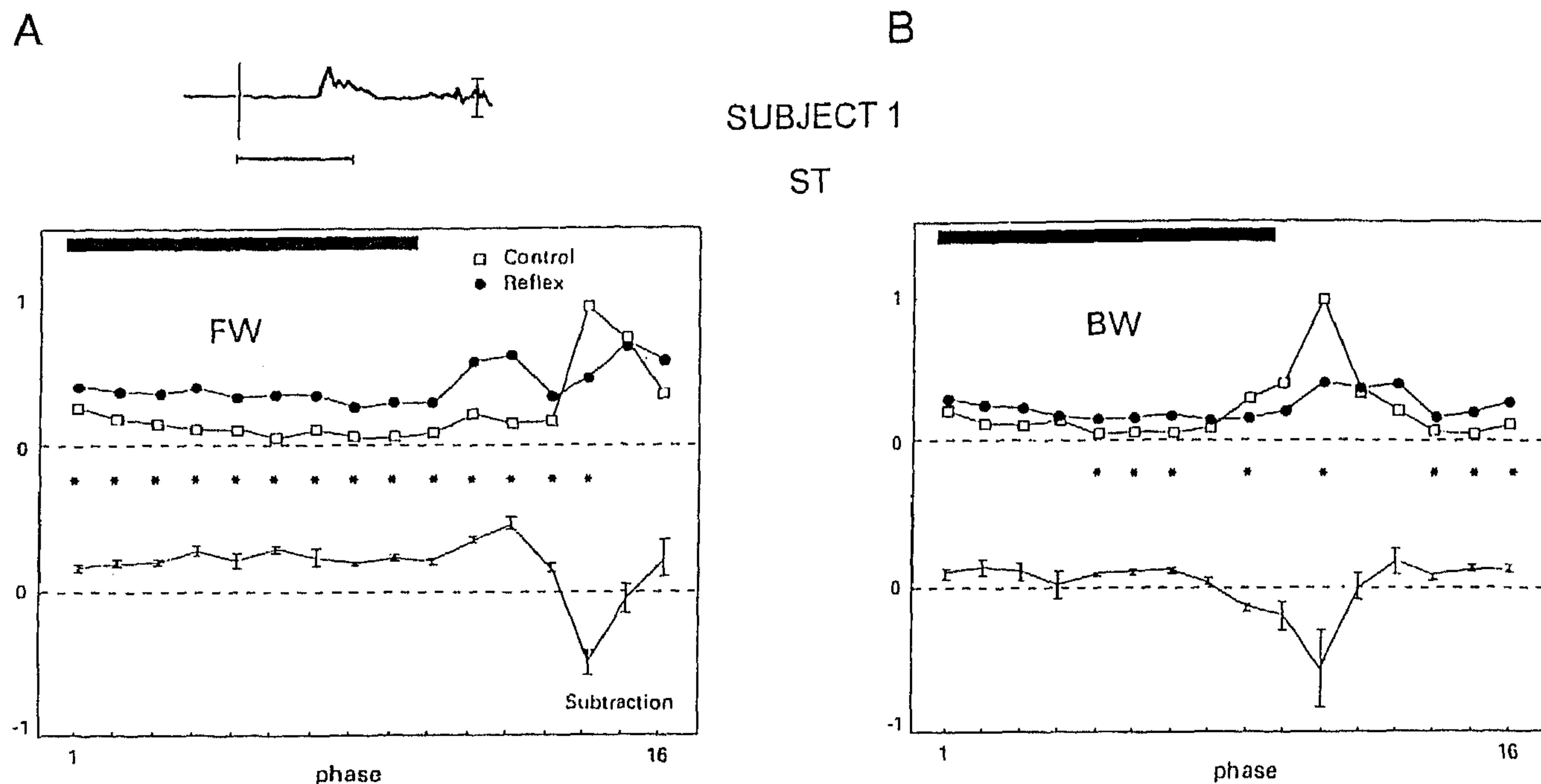


FIG. 1. Phase-dependent modulation of averaged ($n = 10$) measured semitendinosus (ST) medium-latency (P2) responses of 1 subject for forward walking (FW) (left) and backward walking (BW) (right). *Inset*: example of averaged ($N = 10$) subtracted electromyographic (EMG) responses to sural nerve stimulation in a single subject during FW. Solid vertical line: onset of stimulation. *Top graphs*: comparison of control (without stimulation) and reflex (with stimulation) mean EMG as calculated within the P2 windows. The data are normalized with respect to the maximum control activity in the step cycle. The position in the step cycle (in this and all equivalent figures of the present paper) corresponds to the position of the middle of the responses. *Bottom graphs*: same data, but represented as mean subtracted responses with their standard errors. Asterisks: significant facilitation or suppression according to a Wilcoxon matched-pairs signed-rank test (significance $\leq 5\%$) performed on the subtracted values of the individual trials. Dark bar: stance phase. Time scale of *inset* (horizontal bar): 100 ms. EMG calibration: 1 mV.

phases of the step cycle are summarized in Fig. 1, A and B, for *subject 1* during FW and BW, respectively (response window set at 64–106 ms). At the *top* a comparison is made between the reflex (unsubtracted) responses and the control background sample, whereas the difference between these two is plotted at the *bottom* (Subtraction). The background activity of ST shows that ST is mainly active during the second half of the swing phase, where it assists in decelerating the extension of the knee, in preparation of touchdown. In contrast, during BW, this muscle is mainly active during the beginning of the swing phase, where it initiates hip extension and knee flexion needed to start the swing movement of the leg.

As seen in Fig. 1, during FW *subject 1* showed significant

TABLE 1. Average P2 window settings for the whole population

	Onset Latency, ms		End of Window	
	FW	BW	FW	BW
ST	71 \pm 9	74 \pm 7	106 \pm 8	106 \pm 9
BF	68 \pm 10	76 \pm 6	105 \pm 10	110 \pm 7
RF	68 \pm 10	73 \pm 5	105 \pm 10	106 \pm 6
TA	73 \pm 7	76 \pm 6	110 \pm 9	111 \pm 13

Values are means \pm SD. P2, medium latency; FW, forward walking; BW, backward walking; ST, semitendinosus; BF, biceps femoris; RF, rectus femoris; TA, tibialis anterior.

facilitatory responses in ST during the beginning of swing (phases 1–13). Exceptionally, this subject also showed distinct responses throughout the entire stance period (compare *subject 1* with the other subjects in Fig. 2C). At the maximum of spontaneous activity near the end of swing (phase 14), there was a reversal to a significant suppressive response, and during phases 15–16 there was a gradual return to facilitatory responses during stance (Fig. 1).

During BW, *subject 1* had a different modulation pattern than during FW. The subject showed facilitatory responses during the beginning and the middle of the stance phase (phases 1–8), although not as significantly as during FW. At the end of the stance phase there was a reversal toward suppressive responses, lasting throughout the beginning of swing (phases 9–11) and reaching a maximum when the control activity was at its peak (phase 11). During the middle of swing there was a second reversal point, with the response sign changing from suppressive to facilitatory (phase 12). At the end of swing the responses were facilitatory (significant in phases 14–16).

ST responses in the population

In Fig. 2 the mean P2 responses in ST of all subjects (Fig. 2, A and B) and of each individual subject (Fig. 2, C and D) are shown both for FW and BW. The windows, used to measure the responses in the whole group, were set quite similarly as for *subject 1*, namely on average from 71 \pm 9

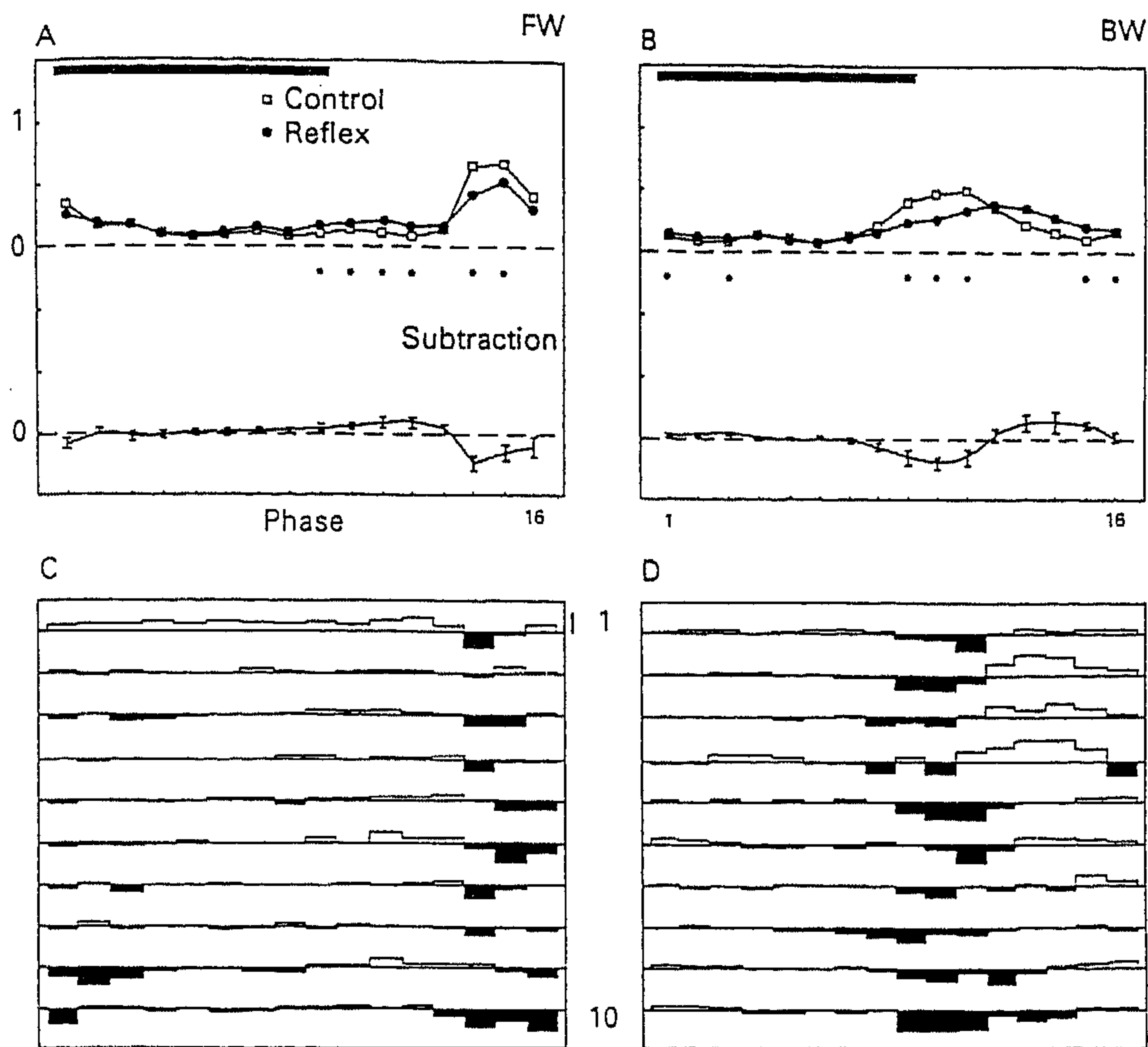


FIG. 2. Phase-dependent modulation of ST responses of 10 subjects for FW (left) and BW (right). A and B: average responses for all subjects ($n = 10$). Data were first normalized for each subject individually. Conventions as in Fig. 1. The significance (asterisks, as in Fig. 1) was tested on the basis of the subtracted responses (A, bottom and B, bottom). Horizontal bar: stance phase. C and D: subtracted averaged ($N = 10$) responses at 16 phases for the 10 subjects individually. Order of phases in C and D is the same as in A and B, respectively. Subjects were ranked according to the sum of the subtracted values of 16 phases, with *subject 1* having the highest amount of facilitatory responses. Open bars (above 0): facilitatory responses. Black bars (below 0): suppressive responses. Calibration: in C and D the small dark vertical bars indicate the maximum level of background activity in the step cycle.

(SD) ms to 106 ± 8 (SD) ms for FW and from 74 ± 7 (SD) ms to 106 ± 9 (SD) ms for BW (Table 1).

For the whole population the responses during most of the stance phase of FW were not significant (Fig. 2A). At the end of stance and during the beginning and the middle of the swing phase there were significant facilitations (phases 9–12) followed by a reversal point at phase 13 to suppressive responses at the end of swing (phases 14–15) in the period of highest control activity.

During BW (Fig. 2B) there were small (but sometimes significant) responses during the beginning and the middle of the stance phase (phases 1–7). After a gradual reversal, suppressive responses started at the end of the stance phase. These suppressive responses reached the $P < 0.05$ significance level in phases 9–11. The suppressive responses lasted until the middle of swing, where a reversal to facilitatory responses occurred (phase 12). The facilitations were present throughout the final part of swing (phases 13–16, significant in phases 15 and 16). Thus again suppressive responses occurred preferentially in the part of the step cycle during which the control activity was highest.

It is clear from Fig. 2, C and D, that the envelope of the modulation pattern was quite similar between subjects. During FW, all subjects showed some suppressive responses in the second half of swing (phases 14–16, Fig. 2C). During BW, all subjects had at least some degree of suppression at the transition from stance to swing (phases 9–11). The facilitatory responses occurred most consistently at the transition from stance to swing during FW (phases 11 and 12) and in the second half of the same phase in BW (phase 15).

For most subjects the levels of the responses and of the

background activity were similar for FW and BW (Fig. 2, A and B), but differences were sometimes seen in individual subjects (*subject 1* in Fig. 2, C and D). The ratio of the averaged BW over FW control activity for all subjects was 1.13 ± 0.12 (SD), indicating a comparable level of spontaneous activation.

Responses in other muscles

A similar analysis was performed for the three other muscles, namely BF, RF, and TA. The latencies for the responses were sufficiently similar for FW and BW to indicate that in both cases P2 responses were observed (Table 1).

BF was active at about the same periods as ST. In Fig. 3 it can be seen that the responses in BF were considerably larger than those in ST both during FW and BW and they were almost always significant.

A reflex reversal did not occur but there was a distinct modulation of the amplitude of the responses. During FW the largest facilitatory subtracted responses were seen in phase 11 during early swing both for *subject 1* and for the whole population. The ratio of the reflex responses over the background activity was smallest in phase 14 in late swing (both for *subject 1* and for the whole population). In this phase the responses were particularly small despite near-maximum background activity (similar to the situation during running; see Tax et al. 1995). During BW the P2 responses were large throughout most of the stance phase and smallest at the onset of the swing phase.

RF (Fig. 4) is a hip flexor and knee extensor. In FW it is active during early stance (to aid in support and prevent

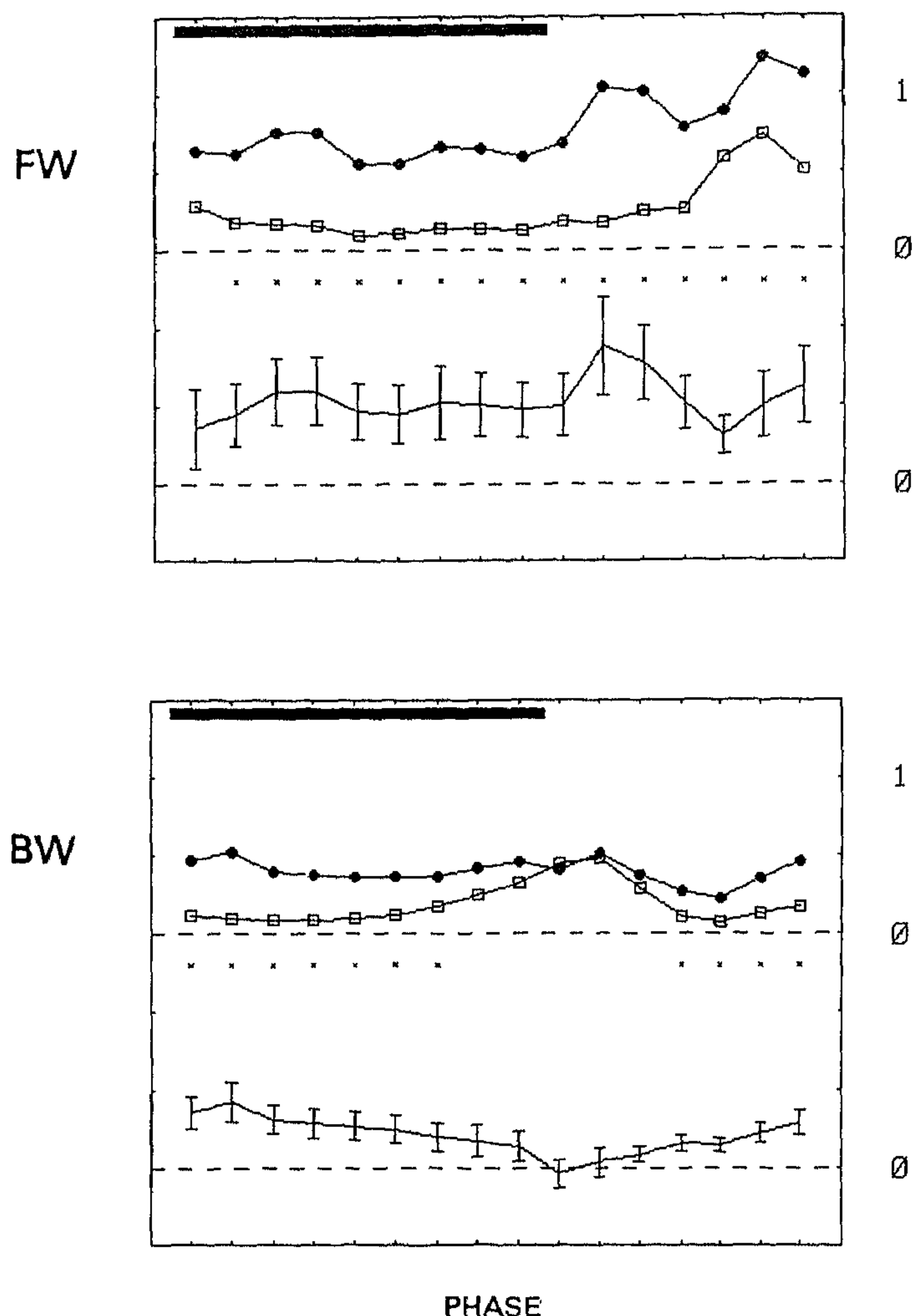


FIG. 3. Phase-dependent modulation of P2 responses in biceps femoris (BF) of the whole population during FW (top) and BW (bottom). Same format as Fig. 2, A and B.

yielding) and at end stance (to initiate hip flexion and aid pushoff). During BW, RF is active in early and middle stance. In RF, the largest facilitatory P2 responses in FW occurred near the transition from stance to swing, whereas the smallest responses were seen in phase 14. In BW the RF responses were largest in the early stance phase and smallest near the transition from stance to swing phase.

TA (Fig. 5) is active throughout the swing phase during FW. It often shows two peaks of activity during FW, one at the transition from stance to swing (ankle flexion) and one at the transition from swing to stance (deceleration of plantar flexion). During BW, TA is active in the second half of stance (to assist rolloff of the foot) and during the swing phase (to maintain ankle flexion). These activity patterns are consistent with those found by others (Kramer and Reid 1981; Thorstensson 1986). In TA the facilitatory P2 reflexes during FW were at a maximum during the first activity period (early swing), whereas the suppressive responses were at a maximum at the end of the swing phase and at the onset of the stance phase. At the end of the swing phase in most subjects there was not only a reduction in the amplitude of the facilitatory TA responses (as seen for *subject 1* in Fig.

5, top) but a reversal to suppressive responses (as described by Duysens et al. 1990; Yang and Stein 1990). Thus the population average showed an overall reversal from significant facilitatory responses in early swing to suppressive responses at end swing during FW. However, such reversal was not observed in the data of all subjects individually (consistent with Duysens et al. 1992b, 1993; and for running see Tax et al. 1995). During BW, the P2 responses in the population were largest in the second half of the swing phase, whereas significant suppressive responses occurred in late stance (phases 7 and 8; Fig. 5, bottom).

Reflex synergy

To summarize the reflex data, the averaged amplitudes of the (subtracted) responses in the various muscles are shown in Fig. 6 for FW and BW. In the subject shown as an example in Fig. 1, there was exceptionally little reversal from facilitatory to suppressive responses in either FW or BW (except for example phase 1 for TA and phase 14 for ST in FW). However, in the average for the whole population such rever-

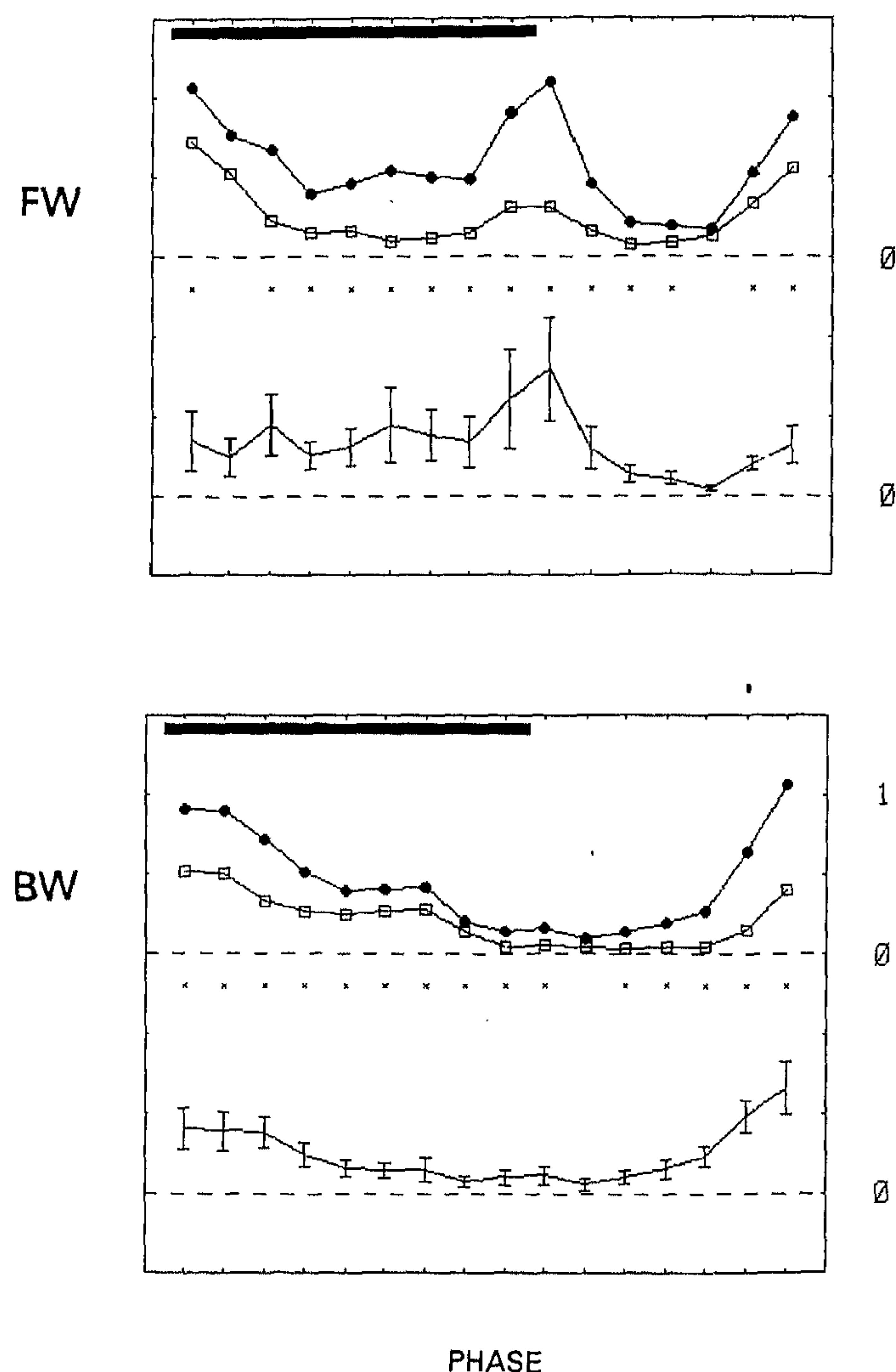


FIG. 4. Phase-dependent modulation of P2 responses in rectus femoris (RF) in the whole population during FW and BW. Same format as Fig. 2, A and B.

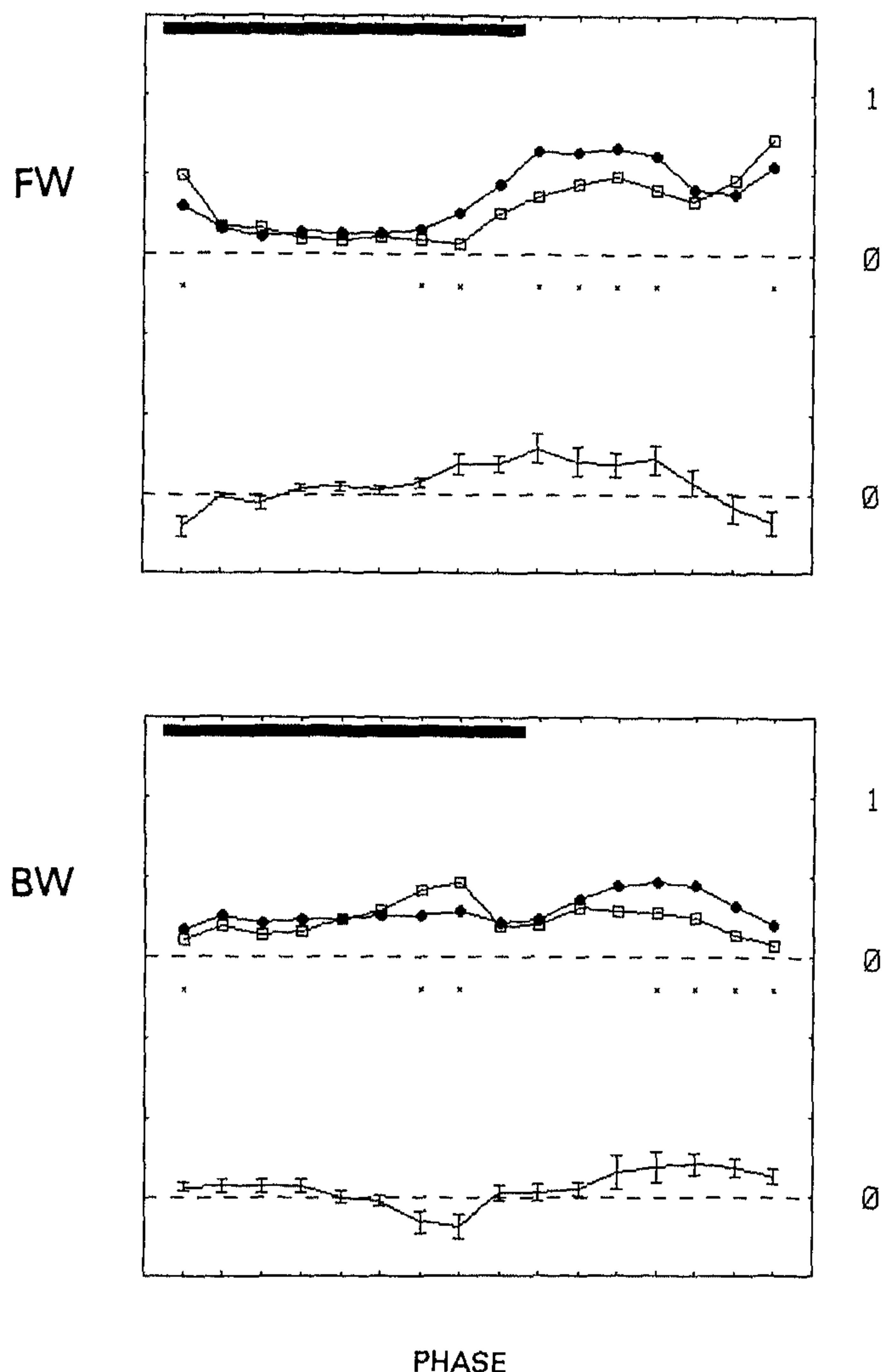


FIG. 5. Phase-dependent modulation of P2 responses in tibialis anterior (TA) in the whole population during FW and BW. Same format as Fig. 2, A and B. Note that for all subjects there are fewer significant data points compared with other muscles (because of larger variability in the population).

sals were prominent. At end swing or during early stance in FW the facilitatory responses were replaced by suppressive P2 responses in both ST and TA. During BW the period of maximum overall facilitatory responses was in the second half of the swing phase. In early stance large responses appeared in BF and RF but not in ST and TA. In late stance the responses in BF and RF were small and those in ST and TA reversed (on average) to suppressive responses. During FW, large facilitatory responses were obtained in all muscles investigated in late stance and early swing both for individual subjects (Fig. 6, A and B) and for the whole group (Fig. 6, C and D). In contrast, near phase 14 in the second part of the swing phase the responses in BF and RF were at a minimum.

DISCUSSION

This investigation concerns the phase-dependent modulation of cutaneously evoked P2 responses in leg muscles during both FW and BW. In humans, this is the first study of

cutaneous reflexes during BW (in cats a similar study was recently performed by Buford and Smith 1993). In general, the presently described activation pattern of the reflexes in the various muscles is in agreement with previously published data on running (Duysens et al. 1992a,b; Tax et al. 1995). With respect to the phase-dependent modulation of these responses, the FW results closely resembled forward running but clear differences were observed for BW. At present it was found that in some muscles such as ST and TA a reversal from facilitatory to suppressive P2 responses was present in both FW and BW, but the reversal had a different sign and occurred at a different time in the step cycle for these two forms of locomotion. Several mechanisms could underlie these results about the phase-dependent modulation.

The first possibility is that the stimulus was not truly constant throughout the step cycle because the movement displaced the electrodes. This issue has been discussed at length in previous publications (Duysens et al. 1995; Tax et al. 1995). In short, when there is displacement because of instability of the electrode, this is always clearly reflected in changes in stimulus current. In previous work it was sometimes necessary to correct for these minor changes (see Duysens et al. 1995). However, for the present series such a correction was not needed simply because the current was stable across step cycle phases (variations of <3%; see METHODS). One may still argue that the current as received by the nerve may have varied. For example, one could propose that the absence of reflexes at end swing during FW could have been due to a reduction in "effective" current. However, it has previously been shown that such reductions in facilitatory responses occur also when M waves remain constant (Yang and Stein 1990). Furthermore, we recently showed that subjects perceive the stimuli in this period as more intense than in any other part of the step cycle (Duysens et al. 1995), which is hard to explain if current was less effective in reaching the nerve. Finally, at end swing during FW and in early swing in BW the changes in ankle angle are relatively small compared with those in other parts of the step cycle (e.g., late stance for FW and early stance for BW, see Thorstensson 1986; Vilensky et al. 1987). There is thus no good reason to suspect that stimulus instability would be at a maximum in those periods when facilitatory responses are smallest.

A second mechanism to explain the results is based on the observation that the amplitude of reflex responses increases when background activity is larger. It was previously shown that this element cannot explain the pattern of modulation of sural nerve induced responses (Duysens et al. 1990, 1991, 1992b, 1993; Tax et al. 1995). Similarly, for BW it is evident that background activation levels cannot predict the amplitude of responses. For example, ST is active throughout swing, yet there are facilitatory responses at end swing and suppressive responses in early swing.

A third factor that may be involved is the anticipation of footfall. This "prefootfall" hypothesis states that the reversal from facilitatory to suppressive responses before footfall in FW (Duysens et al. 1990; Yang and Stein 1990) serves to avoid unwanted perturbation of placement of the foot at this critical moment in the step cycle (see INTRODUCTION). The reversal could then be due to some "voluntary" motor

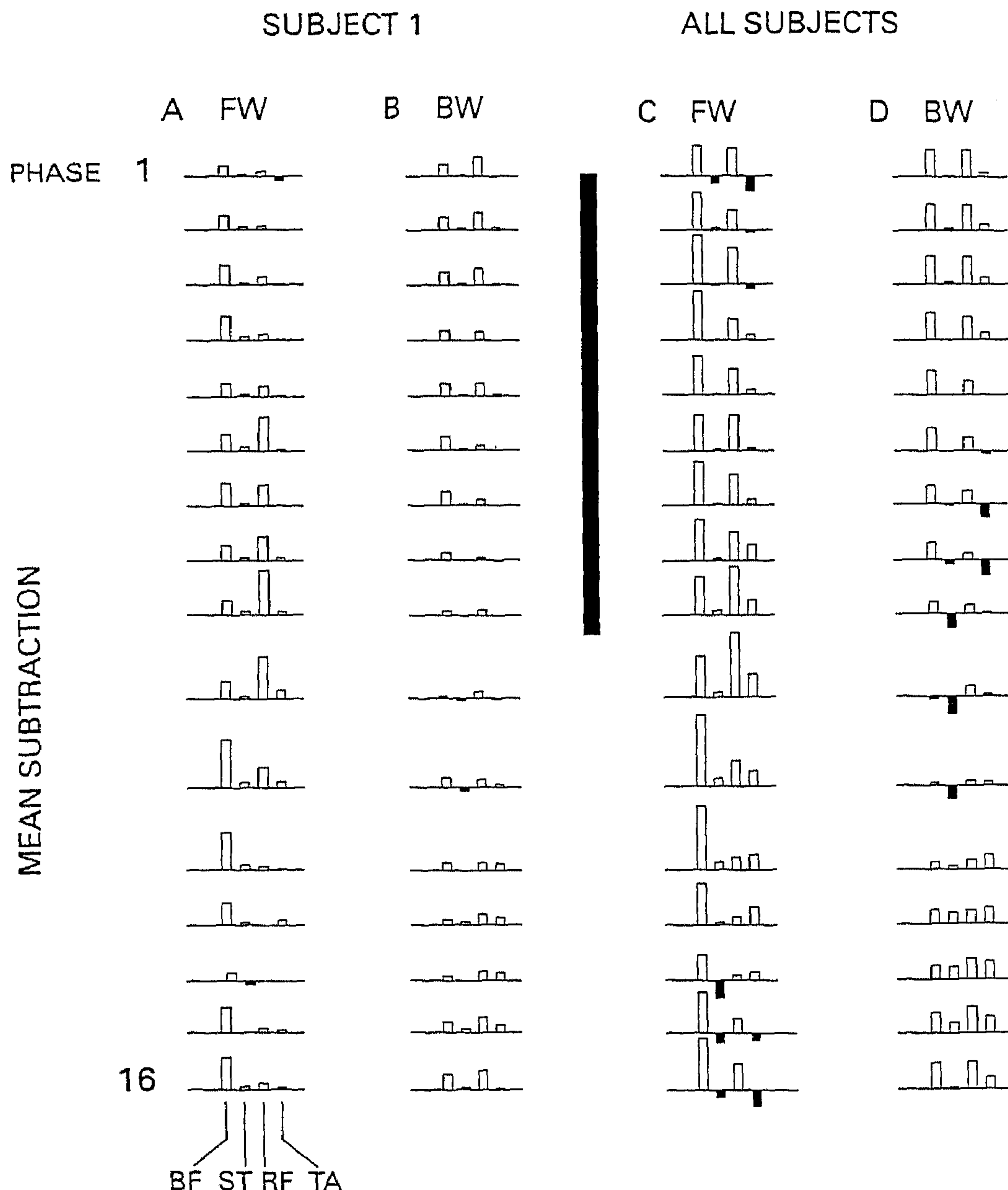


FIG. 6. Summary of phase-dependent modulation of P2 responses for all 4 muscles investigated and for 16 phases of the step cycle. Length of bars: mean subtracted responses. Values >0 : facilitatory responses. Values <0 (black areas): suppressive responses. Vertical bar: stance phase. Calibration: see subtracted data of population plot in Figs. 2–5.

command in anticipation of foot placement. If preparation for landing is an important element for the reversal, one would expect a similar reversal from facilitatory to suppressive responses to occur just before touchdown during BW as well. In reality, this did not occur and in fact the largest facilitatory responses occurred in this period during BW.

A fourth possibility is that the occurrence of suppressive responses is related to afferent feedback related to the position or the movement of the leg. Both at end swing of FW and in late stance in BW the leg is extending except at the hip where maximum flexion is reached. In a previous study based on experiments with limb positions imitating phases of the step cycle, it was shown that static limb position

affected the amplitude of the responses but only insofar as the background EMG covaried (Duysens et al. 1993). However, such static experiments do not exclude the possibility that movement-related feedback can interfere with phase-dependent reflex modulation. In fact, for H reflexes it has recently been shown that passive limb movements are almost as effective as active ones in producing locomotor-related suppression of responses (Brooke et al. 1995). For cutaneous reflexes there is as yet no evidence for a similar suppressive action by passive movements.

According to the fifth hypothesis, the phasic modulation of reflexes during FW is caused centrally through the intervention of a motor program (such as provided by a CPG, for example). If so, then the modulation of cutaneous reflexes

observed during BW is likely to be determined by the same motor program, but working in reverse (see INTRODUCTION). In its most simple form one may think of the locomotor "program" of a single limb as consisting of two parts, one producing stance and one underlying swing. If one assumes that each of these subprograms works in reverse during BW compared with FW, then one would predict that suppressive responses occur in early swing, as was indeed observed for ST and TA, for example. For BF there was no phase-dependent reflex reversal. Thus, instead, the point of "minimum ratio" will be considered (ratio of unsubtracted reflex response over the corresponding background). During BW this ratio is at a minimum during early swing, consistent with the program reversal idea.

If human BW is largely dependent on a central program working "in reverse" then the crucial question is how this is implemented at the neural control level. Support for the hypothesis that modifications of a single neural network can generate opposite motor outputs can be found in several systems (see Dicaprio 1990 for recent review). For the cat it was suggested that a reorganization of connections between separate "unit generators" of hip and knee is required in order to use the FW CPG for BW (Edgerton et al. 1976; Grillner 1981; Grillner and Wallen 1985), but the data on BW of intact cats do not fully support this idea (see INTRODUCTION). Insofar as the present data can be explained by the intervention of a motor program, they do not support a scheme such as proposed for the unit generators. In this scheme in BW the connections between the hip, knee, and ankle are reorganized so that hip extensors would be coactivated with knee and ankle flexors. Likewise, one would then expect that the phase-dependent pattern of reflex activations would be different at these different joints. However, the present data show that the shift of the reversal is very similar for all muscles investigated, irrespective of the joints they span. Thus the present data are more in agreement with the idea of a single CPG used both in FW and BW but working in reverse.

Functional significance of facilitatory P2 responses at end stance

The timing differences in modulation for the different muscles can be summarized by considering two periods, one when the facilitatory responses were at a maximum in the different muscles investigated and one when they were at a minimum.

In all cases of FW studied so far, it was striking that large P2 responses at end stance were present in muscles with a potential flexor function (BF and ST are knee flexors; RF is a hip flexor; TA is an ankle flexor). In accordance with previous work it is therefore proposed that the enhancement of P2 responses before the onset of the swing phase reflects an opening of pathways that could assist flexion in the ensuing swing phase (Duysens and Loeb 1980; Duysens et al. 1992b). For example, it seems likely that interneurons from the flexor reflex afferent system were facilitated at end stance. However, during BW, the period when all muscles with a potential flexor function had large P2 responses corresponded with the middle and end of the swing phase. This may be related to a basic kinesiological difference between

FW and BW in humans. According to Vilensky et al. (1987) the main period of knee flexion is between ~40 and 70% of the step cycle during FW but between 60 and 85% during BW. This later occurrence of knee flexion is because propulsion at end stance is through knee extension in BW and this extension continues till early swing. Because flexion occurs at a later stage in BW than in FW, it is not surprising that flexor assisting pathways are being opened later in the step cycle in BW than in FW.

The idea that flexor reflex afferent pathways are opened at end stance relies on previous suggestions made by Lundberg and coworkers, on the basis of a study on the function of group II muscle afferents (Lundberg et al. 1987; for review see Dietz 1992). These authors proposed that afferent activity from skin and muscle is combined in reflex pathways that are continuously used to assist movements. The crucial point of the current hypothesis is that the circuits described are used both during corrective movements and during normal gait. The present data can be explained by assuming that a central program for locomotion regulates transmission in these cutaneous reflex pathways and works in reverse during backward gait.

We thank M. Trippel, B. van Wezel, U. Rommelt, and U. Mollinger for participation in the preliminary experiments in Freiburg, and H. Kleijnen, A. van Dreumel, and G. Windau for pleasant technical cooperation and expert help in Nijmegen. We also thank A. Wanders and L. Rossen for secretarial assistance.

This work was supported by grants from the Swiss National Science Foundation (No. 31-42899.95), Esprit (Mucom2, BRA6615), the Deutsche Forschungsgemeinschaft (BE 936/4-1), the Bundesministerium fuer Forschung und Technology (01 KL 9402) and Nato (twinning grant 910574).

Address for reprint requests: J. Duysens, Dept. of Medicine, Physics, and Biophysics, University of Nijmegen, Geert Grooteplein Noord 21, 6525 EZ Nijmegen, The Netherlands.

Received 24 October 1995; accepted in final form 24 January 1996.

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