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Research paper

Excitatory and inhibitory responses to cervical root magnetic stimulation in healthy subjects

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ABSTRACT

Objectives: To characterize direct and reflex hand muscle responses to cervical root magnetic stimulation (CRMS) in healthy volunteers during sustained voluntary contraction.
Methods: In 18 healthy volunteers, we recorded from the first dorsal interosseous (FDI) muscle the responses to CRMS of progressively increasing intensity and level of muscle contraction. The compound muscle action potential (CMAP) and the silent period (SP) were compared to those obtained with plexus, midarm and wrist stimulation. Additionally, in a smaller number of subjects, we obtained the peristimulus time histogram (psth) of single motor unit firing in the FDI, examined the effects of vibration and recorded the modulation of sustained EMG activity in muscles of the lower limbs.
Results: Increasing CRMS intensity led to larger CMAP with no relevant changes in SP1 or SP2, except for lower amplitude of the burst interrupting the silent period (BISP). Increasing the level of muscle contraction led to reduced CMAP, shorter SP duration and increased BISP amplitude. The psth analysis showed the underlying changes in the motor unit firing frequency that corresponded to the changes seen in the CMAP and the SP with surface recordings. Progressively distal stimulation led to CMAPs of shorter latency and increased amplitude, SPs of longer latency and shorter duration, and a BISP of longer latency. Vibration led to reduction of the SP. CRMS induced SPs in muscles of the lower limb.
Conclusions: CRMS induces excitatory and inhibitory responses in hand muscles, fitting with the expected behavior of mixed nerve stimulation at very proximal sites.
Significance: Characterization of the effects of CRMS on hand muscles is of physiological and potentially clinical applicability, as it is a painless and reliable procedure.

1. Introduction

Magnetic stimulation has been used for many years to induce experimentally controlled activation of the nervous tissue. It is preferred over electrical shocks for stimulation of neural tissue lying deep under thick bony structures, as in the case of transcranial magnetic stimulation. Magnetic stimulation is painless, as it avoids the activation of small nerve fibres in the skin and subcutaneous tissues that would occur if high intensity electrical current were employed (Groppa et al., 2012). Magnetic stimulation can also be used for activation of peripheral nerves, including roots and plexuses, albeit it has less focality and precision than electrical stimulation (Maccabee et al., 1988; Olney et al., 1990). Magnetic stimulation of the roots at the cervical column (Cervical Root Magnetic Stimulation, CRMS) is commonly used for the assessment of central motor conduction time, undoubtedly the most valuable measure obtained with magnetic stimulation for clinical practice (Groppa et al., 2012; Udupa and Chen, 2013). However, there is relatively little research done with root stimulation. In early studies, Ugawa et al. (1989) showed that CRMS activated the motor axons at the spinal roots, the same site as they are activated by electrical stimulation. Chokroverty et al. (1991) showed how conduction time measured with CRMS differed from that measured through the F wave. Epstein et al. (1991) used a focal coil and low intensity stimulation to demonstrate that the site where compound muscle action potentials (CMAP) were generated by CRMS was at root level in the intervertebral foramina. Zwarts (1993) pointed out that CRMS activates also sensory fibres at the dorsal root ganglion. More recently, it has been demonstrated that CRMS intensity can be supramaximal for the generation of CMAPs (Matsumoto et al., 2010).

CRMS activates motor and sensory axons at root level. Therefore, the responses recorded in hand muscles may arise not only

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from the orthodromic volley generated in motor axons but also by the sensory volley via reflex activation of the motoneurons and by the antidromic volley that may either collide with the descending inputs in a variable proportion depending on the level of voluntary contraction. The effects induced by CRMS in hand muscles may be similar to those induced by mixed nerve stimulation at distal nerve sites (Leis et al., 1991; Deuschl and Lücking, 1990; Cruccu and Deuschl, 2000). With such setup, authors have characterized the electrically induced mixed nerve silent period (mnSP), which, apart from showing a transient decrease of EMG activity, features interrupting bursts ('bursts interrupting the silent period', BISPs) related to excitatory events, and ends up with a rebound excitation (Kimura, 1977; Deuschl and Lücking, 1990, Kumru et al., 2009). While these events should occur with stimulation of any mixed nerve, they have not been characterized so far when stimulation is applied at root level.

Root stimulation has some interesting particularities, such as activation of motor and sensory axons very close to the alpha motoneurons and to the dorsal root entry zone at the spinal cord. These makes a difference with respect to wrist stimulation, because of longer axonal stretch between stimulation and recording sites and a shorter one between stimulation site and the motoneurons. While this could simply cause a change in latency of the expected events (mnSP and BISPs), there may also be other consequences because of the reduced opportunities for collision between stimulation induced antidromic inputs and the motoneuron output generated during contraction. Therefore, we considered worth a study to characterize the events induced by CRMS of varying intensity on the first dorsal interosseous muscle (FDI) at rest and during a predetermined percentage of maximal voluntary contraction (MVC).

2. Methods

The study was done in 18 healthy subjects (age range 30 to 68; 8 females), who volunteered for the exam. They signed an informed consent for the study, which was approved by the Ethics Committee of the Hospital Clinic of Barcelona.

2.1. Recording and stimuli

All recordings were obtained with a KeyPoint electromyograph, used also to trigger all stimuli. The default setup was a sweep duration of 300 ms and a gain of 1 mV/div. Magnetic stimuli were delivered using a MagStim200 (Almevan, S.A., Madrid, Spain), equipped with a standard 90 mm round coil. Stimuli were applied at 10% delay with respect to sweep onset (30 ms). The EMG signal was obtained with a band-pass frequency filter between 20 Hz and 1000 Hz. To ensure robustness of the observations and comparability between responses, we collected 10 artefact-free rectified traces for each experimental condition, which were saved for off-line analysis.

2.2. Procedure

Subjects were sitting on a comfortable chair, with surface recording electrodes attached over the first dorsal interosseous (FDI) of both sides. With the subjects at rest, we first recorded the supramaximal intensity FDI CMAP by applying electrical stimuli to the ulnar nerve at the wrist. The amplitude of this CMAP was used as the reference value the analyses of all responses (see below). A round magnetic coil was placed with the centre between the T2 and the T3 spinous processes, in such a way that the upper part of the coil was approximately over the C6-C7 roots. The exact coil position was determined while assessing the resting motor threshold (RMT) at onset of all experiments and kept the same for the rest of the session. We defined RMT as the lowest intensity of the magnetic stimulator required to obtain a CMAP of at least 100 μV peak-to-peak amplitude in at least 50% of the stimuli in the targeted FDI. Once the RMT was determined, we set the recording to rectified mode and started the study protocol.

Both coil faces (A and B) were tested at rest. We recorded the CMAPs to CRMS simultaneously from both sides to step increments of 20% RMT stimulus intensity until there was no further increase in the amplitude of CMAP or we reached the maximum stimulator output (100%). For the rest of the study, we recorded only unilateral responses from the side showing the largest responses at rest. In short, the study protocol consisted in obtaining the recruitment curves for the CMAP and all subsequent events to step by step increments of stimulus intensity, level of muscle contraction and stimulation sites along the upper limb.

2.3. Effects of stimulus intensity during muscle contraction

Subjects were requested to exert a voluntary contraction of the FDI by raising the index finger against their thumb. For this experiment, the level of muscle contraction was requested to be about 50% MVC. Stimuli were applied to CRMS at progressively increasing intensity, as in the study at rest, in step increments of 20% RMT.

2.4. Effects of increasing the degree of muscle contraction

The effects of voluntary contraction were studied by requesting subjects to maintain a voluntary contraction at either 25%, 50%, 75% or 100% MVC while CRMS intensity was kept at 200% of RMT. Auditory and visual feedback of EMG activity allowed the subject to maintain a steady level of MVC. For the 100% MVC, subjects were requested to do their maximum while the stimulus was applied, and rest to prevent fatigue until preparation for the next stimulus. A period of rest was always granted in other levels of muscle contraction when requested by the volunteer.

2.5. Effects of progressively distal stimulation sites

For comparison with the recordings to CRMS, we recorded FDI responses to magnetic stimuli at an intensity of 200% RMT to sites along the upper limb while subjects were maintaining a voluntary contraction of about 50% MVC. The brachial plexus was stimulated with the coil held vertical (handle up) and its edge touching the upper part of the clavicle. Magnetic stimuli were also applied to the ulnar nerve at midarm with the coil held perpendicular to the middle third of the ventral side of the upper arm. Finally, the ulnar nerve was stimulated at the wrist with electrical shocks to obtain the reference CMAP, which size (with the muscle at rest) was used as the 100% for comparison to responses obtained to all other stimulation sites. The stimulus intensity used for these stimulation sites was 200% RMT for CRMS and the level of muscle contraction maintained during stimulation was 50% MVC.

2.6. Additional experiments

Three additional experiments were carried out in a subgroup of 8 volunteers (age range 30 to 68; 3 women), who participated in different numbers:

2.6.1. Effects of extra sensory inputs

We aimed at knowing if responses to CRMS would be affected by sensory inputs. To do that, we analysed the effects of vibratory stimuli, applied with a commercially available vibratory stimulator (PM-30CTM, HoMedics, Barcelona) to the ventral forearm at 80 Hz, on the responses to CRMS. The test was done in 5 subjects (1

woman), who maintained a 50% MVC. Responses were recorded to CRMS at an intensity 200% RMT without and with vibration.

2.6.2. Responses of distant muscles

We aimed at knowing if CRMS had any effect on muscles of the lower limbs and if such effects were any different from the effects of brachial plexus stimulation. To do that, we attached recording electrodes over the tibialis anterior (TA) of both sides in 6 subjects (3 women) and recorded responses at rest and during maintenance of a moderate to strong contraction of the TA by performing a dorsiflexion of the foot against an external resistance. Stimulation intensity was 200% RMT for CRMS, applied to the cervical site and the brachial plexus.

2.6.3. Effects on single motor units

We aimed at evaluating the effects of CRMS on single motor unit action potentials during low-level voluntary muscle contraction. To do that, we generated a peristimulus time histograms (psth) after recording motor unit action potentials with a needle electrode inserted in the FDI. The study was done in 2 volunteers (1 men and 1 woman), who trained for some time until being able to activate as steadily as possible a single motor unit. When this was considered feasible, we applied CRMS at an intensity around RMT in such a way that some of the selected motor units were activated at the expected CMAP latency and others were not. We recorded a minimum of 100 epochs of 1 s for each motor unit. CRMS was applied at the middle of the epoch, 500 ms after onset of recording.

2.7. Outcome measures

The analysis of responses focused on three events: CMAP, SPs and BISPs. We measured these events in the waveforms resulting after averaging the 10 rectified traces recorded for each test, with a minimum amplifier gain of 100 μV per division. Presence of the event was considered when it could be identified in at least 5 out of the 10 trials at its expected latency (i.e., we did not consider unclear events appearing in a few traces or in the averaged waveform if they were not consistently seen during the recording, as they were judged to be a spurious interference).

At rest, only the CMAP was considered. Peak latency was measured in ms from the stimulus artefact to the first peak of the rectified averaged CMAP. Peak amplitude was measured in μV from baseline to the tallest peak of the averaged waveform. During contraction, latencies were also measured from the stimulus artefact, while size of the CMAP and of all other events recorded were measured with respect to the level of pre-stimulus EMG activity, determined as the mean value of the background EMG activity in the 30 ms preceding stimulus application. A SP was considered when the mean EMG level dropped to more than 80% of the background for at least 10 ms. We measured SP onset latency at the time in which the EMG activity crossed the 80% of the mean background EMG level, and SP duration as the time from onset latency to when the EMG activity raised back to 80% of the mean background EMG level. SP depth was not measured. A BISP was considered when there was a burst of EMG activity interrupting the SP which peak amplitude was larger than 80% of the mean background EMG level. BISP's latency was measured at the peak, while duration was measured from the time at which the activity crossed the 80% of the background level to the time at which the activity decreased to less than 80% of the mean background level. BISP's peak amplitude was measured in percentage of the mean background EMG level, regardless of the depth of the SP in which the BISP was implanted. In this way, a value of 100% would correspond to a BISP which peak amplitude reached exactly the mean background level. A schematic diagram is shown in Fig. 1 as an explanation of the methods used for measuring all the events observed at rest and during contraction. We did not analyse the rebound phenomenon usually seen at the end of the SP, which has been considered an unspecific reaction composed of various phenomena (Manconi et al., 1998; Kumru et al., 2009), nor the F wave that was expected to wrist stimulation.

Results from the additional experiments 1 and 2 were analysed in the way described above, in the same FDI in experiment 1 during vibration, and in the TA in experiment 2. In experiment 3, we obtained 100 traces of 1 s duration with a number of motor unit action potentials in each of them. We basically counted the number of action potentials firing at each ms in each trace for the pre-stimulus and the post-stimulus epochs and plotted these numbers as psth. Results will be just described, as the few subjects involved prevented a group analysis.

2.8. Data presentation and statistical analysis

Data are reported using descriptive statistics for the mean and standard deviation (SD) of each of the events measured in the various experimental conditions. In case of absence of data for a specific event, neither latency nor amplitude or duration were entered into the calculation. For statistical purposes, we normalized individual's data on response amplitude as percentages. For the CMAP amplitude, we considered 100% the peak amplitude of the rectified response obtained to supramaximal intensity electrical stimulation of the ulnar nerve at the wrist. For the SP and BISP, we considered 100% the background level of EMG activity during the 30 ms preceding the stimulus.

Comparative statistics were used for evaluation of differences within and between conditions. Since the response configuration would differ between rest and contraction, comparisons were done separately. We used paired t-tests for comparison of data at rest: the CMAP amplitude between sides, and the amplitudes of the CMAPs obtained to CRMS and to wrist electrical stimulation. Data obtained during muscle contraction, i.e., peak amplitude and peak latency, were grouped according to the experimental condition. We used the one-factor repeated measures ANOVA to analyse the effects of stimulus intensity on responses to CRMS at 50% MVC, and the effects of the strength of muscle contraction on responses to CRMS at 200% RMT stimulus intensity. These results were compared to those of stimulation in other sites along the upper limb at the same intensity and level of muscle contraction. The Bonferroni's post-hoc analysis was applied when results of the ANOVA comparison were significant at $p < 0.05$.

3. Results

We obtained responses to CRMS in all subjects. There were neither dropouts nor undesired effects and no traces had to be rejected in the off-line analyses because of artifacts or unsuitable recordings.

3.1. CMAPs at rest

As expected, peak latencies and amplitudes varied according to the coil's face applied to the cervical cord. RMT was lower, and peak amplitudes at any stimulation intensity were larger, for the right FDI with coil current flowing clockwise, and for the left FDI with coil current flowing anticlockwise, than for the contralateral responses. Consequently, for the rest of the study, we limited the recording and analyses to the right FDI responses to face B of the coil (current flowing clockwise). In Table 1, we report data on the RMT and on the peak latency and peak amplitude obtained with stimuli of the same intensity with the coil current flowing in either

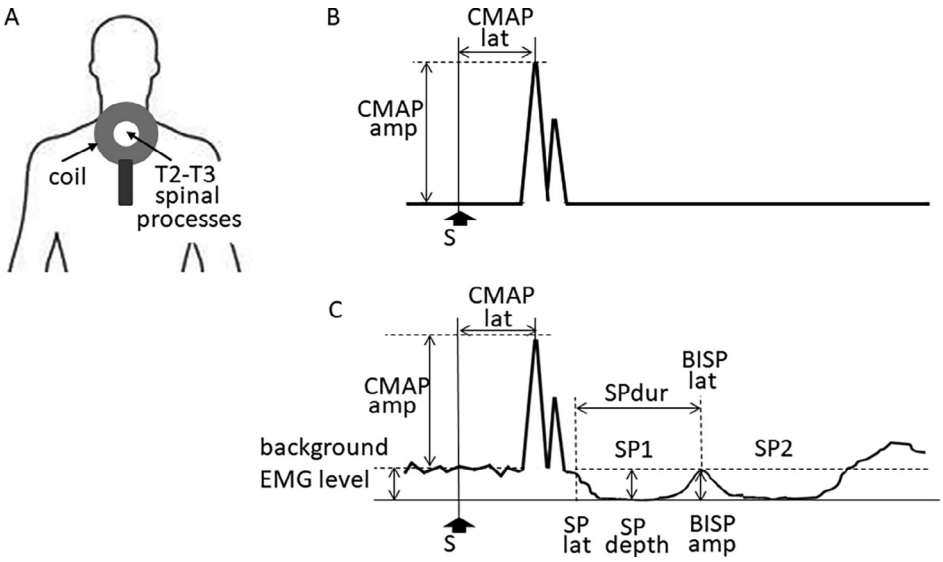

Fig. 1. A: Sketch of the coil position during the experimental sessions. B and C: Schematic drawing of the responses obtained to cervical magnetic stimulation in the right first dorsal interosseous muscle at rest (B) and during contraction (C), labelled with the acronyms indicating the measures taken at each recording: CMAP amp = Compound muscle action potential peak amplitude; CMAP lat = Compound muscle action potential peak latency; EMG = electromyography; SP lat: Silent period onset latency; SPdur: Silent period total duration; BISP size: Burst interrupting the silent period amplitude, measured with respect to the level of EMG background. Only measuring details for the SP1 are marked to avoid confusion, but the same measures were taken for the SP2.

Table 1
Data on CMAP at rest.

		clockwise		anticlockwise	
		right FDI	left FDI	right FDI	left FDI
RMT (%)		25.4 (3.5)	46.1 (11.8)*	45.9 (10.4)	25.5 (3.8)*
Peak latency (ms)	RMT	16.3 (0.9)	16.1 (0.8)	16.3 (0.8)	16.1 (0.8)
	200%RMT	15.2 (0.4)	15.0 (0.6)	14.9 (0.5)	15.3 (0.5)
	Max stim	14.9 (0.3)	14.9 (0.4)	14.8 (0.4)	14.8 (0.4)
Peak amplitude (μV)	RMT	0.1 (0.1)	–	–	0.1 (0.1)
	200%RMT	3.4 (0.6)	0.2 (0.2)*	0.3 (0.2)	3.3 (0.6)*
	Max stim	9.9 (0.9)	1.1 (0.7)*	1.2 (0.8)	9.8 (0.8)*

Figures are the mean and one standard deviation of the resting motor threshold (RMT), given in percentage of the maximum stimulator output, and peak latency (in ms) and peak amplitude (in μV) of the responses obtained in both sides with stimulus intensities calculated for the right FDI when the current in the coil was flowing clockwise and anticlockwise at RMT (RMT), 200% RMT (200%RMT) and the individual's maximum stimulation intensity applied (Max stim).
*= Significantly different in comparison to the contralateral response.

direction. Fig. 2 shows the steady increase in CMAP amplitude and the slight decrease in CMAP peak latency of the right FDI with increasing stimulus intensity when the current in the coil flowed clockwise. The mean number of stimulation steps that we used to reach a stimulation intensity after which there was no further increase in the amplitude of the CMAP was 8.6 (range 5 to 13; median 8). This occurred at a mean intensity of 76% (SD = 8%; range: 68% to 94%), when the absolute value of the CMAP peak amplitude to CRMS (9.9 mV ± 0.9 mV) was not different from that of the CMAP obtained with wrist stimulation in the same subject (10.3 mV ± 0.9 mV).

3.2. Events recorded during muscle contraction

The level of background EMG activity reached with each step of muscle contraction was variable between subjects but, as expected, increased progressively with the strength of muscle contraction. The group absolute values were mean = 0.098 μV and SD = 0.016 μV at 25%, mean = 0.281 and SD = 0.018 at 50%, mean = 0.392 and SD = 0.023 at 75%, and mean = 0.573 and SD = 0.082 at 100%. At all stimulation sites and with all stimulation intensities and levels of muscle contraction, we obtained a CMAP, followed by a brief silent period (SP1), a BISP, and a second silent period (SP2), which was usually longer than SP1 and ended with a rebound. This pattern was present to most stimulation intensities, strengths of muscle contraction and stimulation sites, but was better defined at mild intensities of stimulation, i.e., 200% RMT (Fig. 3), and with mid to high strengths of muscle contraction, 50% to 100% (Fig. 4). Data for all the events are summarized in Tables 2–4. Because of protocol, data on 200% RMT for CRMS at 50% voluntary contraction are repeated in the three tables.

3.2.1. Effects of stimulus intensity

Examples of representative recordings to CRMS are shown in Fig. 3 and numeric data are summarized in Table 2 for selected intensities. The increase of intensity led to a progressive increase of CMAP amplitude, with no significant change in peak latency. The rest of the events were undefined with low intensity stimulation. The mean percentage RMT value at which SP1 could be measured was 143% (SD = 13%). Thence, SP1 onset latency and duration remained with no significant changes. BISP could be first measured at stimulus intensities of 128% (SD = 15%). Its amplitude progressively increased in all subjects up to mean values above 100% at the intensity of 200% RMT. Then, it decreased and even disappeared in some subjects at the maximum stimulation intensity. The SP2 was measurable before SP1, at a mean percentage RMT

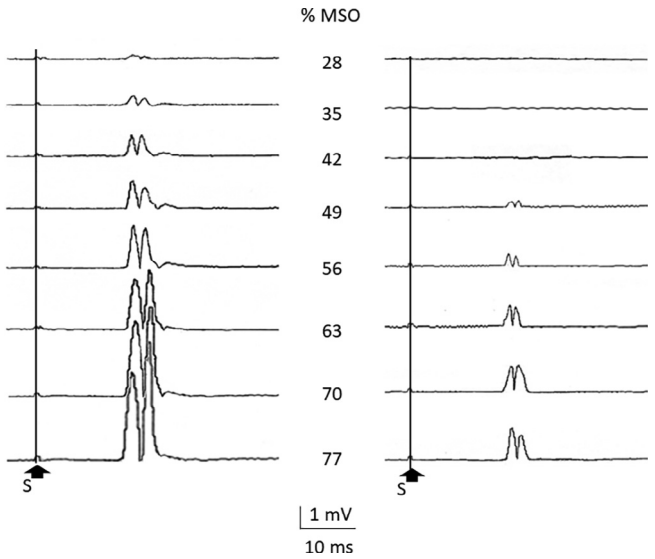

Fig. 2. CMAPs recorded from the right FDI to CRMS at rest using round coil face B (left side of the figure) and face A (right side of the figure). Numbers in the middle column indicate the stimulus intensity used for each recording, beginning at threshold intensity for face B. Note the progressive increase of peak amplitude when stimulating with face coil B, and the differences in threshold with respect to the recordings obtained when stimulating with coil face A. Each of the graphs shown in this figure and in the ones to follow result from averaging 10 rectified responses.

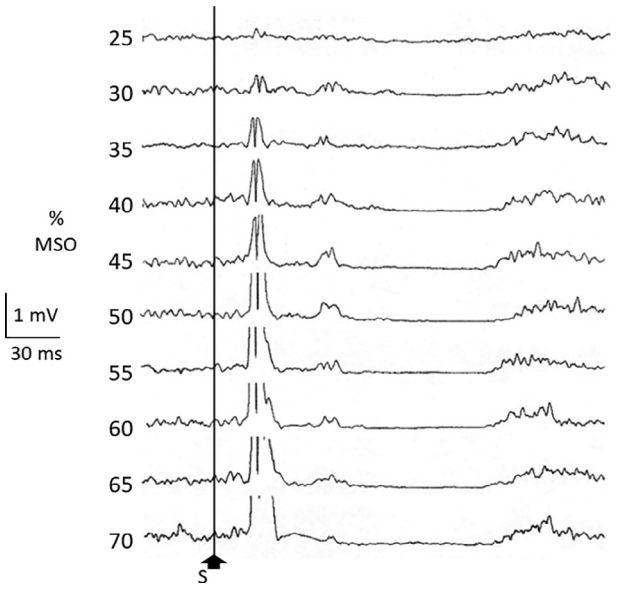

Fig. 3. Responses recorded from the right FDI to CRMS during sustained voluntary FDI contraction at 50% MVC. CRMS intensity was progressively increased from threshold to the intensity at which the maximum amplitude CMAP was obtained at rest (in this case, 70%). Note the progressive initial increase and late decrease of the BISP, without significant changes in the SPs.

intensity of 132% (SD = 12%). It was significantly longer than the SP1 at all stimulation intensities (ANOVA; $F[1,9] = 0.94$; $p < 0.05$), with no changes in duration or latency with increasing stimulus intensity.

3.2.2. Effects of muscle contraction

Examples of representative recordings are shown in Fig. 4 and numeric data are summarized in Table 3. There were no changes in CMAP peak latency related to strength. However, there was a

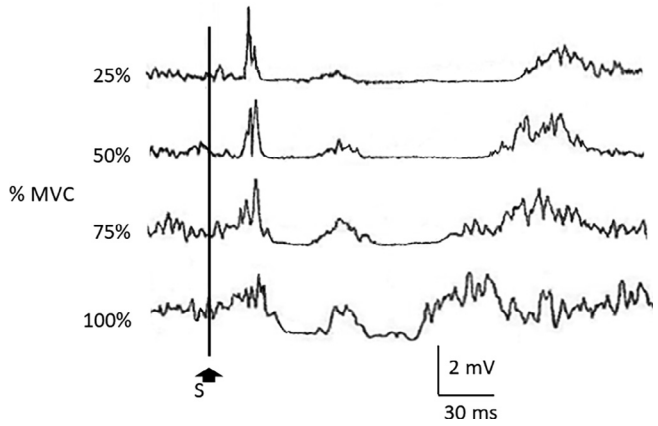

Fig. 4. Responses recorded from the right FDI to CRMS at an intensity 200% RMT during sustained voluntary FDI contraction at progressively higher percentages of the MVC (25%, 50%, 75% and 100%). Note the progressive decrease of the CMAP amplitude, latency shortening of BISP, and decrease of duration in the SPs, with increasing levels of muscle contraction.

slight but significant decrease in CMAP peak amplitude (ANOVA; $F[1,3] = 6.8$; $p < 0.05$), which was due to decreased amplitude at 100% MVC with respect to 25% MVC. The SP1, BISP and SP2 were discernible at low levels of muscle contraction in only 8 out of the 18 subjects examined, but they were apparent in all subjects at 50% MVC and beyond. Increasing the strength of muscle contraction caused a significant delay of SP1 onset latency ($F[1,3] = 18.6$; $p = 0.001$) and a significant decrease of SP1 duration

($F[1,3] = 23.4$; $p = 0.002$). The BISP was clearly distinguishable with mild to strong muscle contraction. Its peak amplitude, though, was kept similar at all levels of muscle contraction, reaching values of around 100% (Table 3). SP2 onset latency did not vary, but SP2 duration markedly shortened with increasing the strength of muscle contraction (ANOVA; $F[1,3] = 6.1$; $p = 0.017$).

3.2.3. Effects of stimulation site

Examples of representative recordings are shown in Fig. 5 and numerical data are summarized in Table 4. As expected, application of stimuli to progressively more distal sites caused CMAP peak latency to shorten and peak amplitude to grow. The effects were significant (ANOVA, $F[1,3] = 98.4$; $p < 0.001$ for latency and $F = 116.3$; $p < 0.001$ for amplitude) among all stimulation sites. The SP1 latency was longer with plexus stimulation than with cervical stimulation, which, as can be seen in Fig. 5, was accompanied by a wider CMAP than with cervical stimulation. With stimulation at midarm and wrist, an additional burst compatible with the F wave, as it did not appear with low stimulus intensities (data not reported) was clearly separated from the CMAP, interrupting the SP1. The F wave had a very variable peak amplitude between 45% and 130% of the background EMG level. With midarm stimulation, the decrease of EMG activity between the CMAP and the F wave did not reach the duration criterion for SP and, therefore, SP1 onset latency was measured after the F wave. With wrist stimulation, the F wave had a mean peak latency of 37.2 ms (SD = 2.8 ms) and the SP preceding the F wave had a mean duration of 13.4 ms (SD = 3.1 ms). The values given in Table 4 correspond to the last part of the SP1, i.e., neglecting the presence of the silent period between the CMAP and the F wave, for simplicity of reporting. There was a significant increase in BISP's peak latency and SP2 onset latency with distal stimulation (ANOVA; $F[1,3] = 4.3$; $p = 0.021$ for BISP's latency and $F = 5.2$; $p = 0.013$ for SP2 onset latency). There were no significant changes in BISP amplitude (ANOVA; $F[1,3] = 0.71$) while SP2 duration was shorter to wrist

Table 2
Data obtained with increasing stimulus intensity when subjects maintained a muscle contraction of 50% MVC.

Stimulus intensity	CMAP		SP1		BISP		SP2	
	Latency (ms)	Amplitude (%)	Latency (ms)	Duration (ms)	Latency (ms)	Amplitude (%)	Latency (ms)	Duration (ms)
RMT	25.3 (2.9)	1.1 (0.6)	–	–	–	–	–	–
140%RMT	24.7 (1.3)	17.9 (10.4)	43.3 (11.4)	11.1 (7.2)	63.1 (7.2)	103.1 (7.5)	88.5 (14.1)	76.2 (13.2)
200%RMT	24.1 (1.0)	30.6 (7.4)	40.8 (8.1)	20.3 (6.9)	62.4 (9.8)	119.2 (10.5)	88.5 (10.9)	77.9 (10.7)
240%RMT	23.9 (0.9)	69.8 (5.3)	41.4 (7.9)	20.2 (5.1)	62.9 (10.7)	98.7 (14.1)	91.4 (17.3)	80.8 (12.8)
Max	22.7 (0.9)	96.2 (6.1)	40.5 (7.7)	21.1 (5.5)	62.7 (6.9)	83.2 (13.9)	87.9 (19.5)	83.3 (10.4)

Figures are the mean and one standard deviation (within parenthesis). MVC = Maximum voluntary contraction. RMT = Resting motor threshold; Max = Individual's maximum stimulus intensity. In this and the remaining tables, CMAP = Compound muscle action potential; SP1 = First silent period; BISP = Burst interrupting the silent period; SP2 = Second silent period. CMAP peak amplitude is expressed as percentage of the CMAP to electrical stimulation of the ulnar nerve at the wrist, while BISP peak amplitude is expressed as percentage of the pre-stimulus background EMG activity. See text for further details.

Table 3
Data obtained with increasing percentage of maximum voluntary contraction with a stimulus intensity of 200% RMT.

Muscle contraction (% MVC)	CMAP		SP1		BISP		SP2	
	Latency (ms)	Amplitude (%)	Latency (ms)	Duration (ms)	Latency (ms)	Amplitude (%)	Latency (ms)	Duration (ms)
25%	16.5 (0.4)	33.9 (4.5)	36.3 (9.4)	24.1 (3.2)	61.5 (8.1)	94.1 (12.6)	81.5 (10.1)	86.2 (13.2)
50%	24.1 (1.0)	30.6 (7.4)	40.8 (8.1)	20.3 (6.9)	62.4 (9.8)	119.2 (10.5)	88.5 (10.9)	77.9 (10.7)
75%	16.1 (0.3)	24.2 (3.4)	41.4 (8.4)	17.2 (4.1)	59.7 (7.4)	104.7 (9.1)	76.4 (7.3)	52.8 (12.8)
100%	16.1 (0.3)	21.8 (3.3)	42.3 (9.9)	12.4 (3.5)	55.8 (6.9)	105.2 (10.9)	71.9 (9.5)	37.3 (10.4)

Figures are the mean and one standard deviation (within parenthesis). MVC = Maximum voluntary contraction. RMT = Resting motor threshold. Column acronyms equal to those of Table 1. See text for further details.

Table 4
Data obtained with stimulation at the specified points along the upper limb with a stimulus intensity of 200% RMT, during maintenance of a muscle contraction of 50% MVC.

Stimulation site	CMAP		SP1		BISP		SP2	
	Latency (ms)	Amplitude (%)	Latency (ms)	Duration (ms)	Latency (ms)	Amplitude (%)	Latency (ms)	Duration (ms)
Cervical	24.1 (1.0)	30.6 (7.4)	40.8 (8.1)	20.3 (6.9)	62.4 (9.8)	119.2 (10.5)	88.5 (10.9)	77.9 (10.7)
Plexus	19.7 (0.9)	43.8 (8.3)	41.2 (10.1)	17.2 (3.9)	60.9 (11.8)	107.2 (5.9)	90.5 (12.6)	72.3 (10.7)
Midarm	12.4 (0.8)	63.0 (9.4)	36.6 (6.8)	15.7 (4.9)	62.3 (9.7)	101.7 (7.1)	92.4 (11.2)	67.8 (12.8)
Wrist	7.3 (0.5)	80.7 (10.3)	39.3 (4.9)*	14.4 (3.8)*	61.2 (10.9)	99.2 (13.9)	97.9 (13.1)	61.3 (10.4)

* Values obtained by neglecting the presence of the silent period between the CMAP and the F wave. See text for further details.

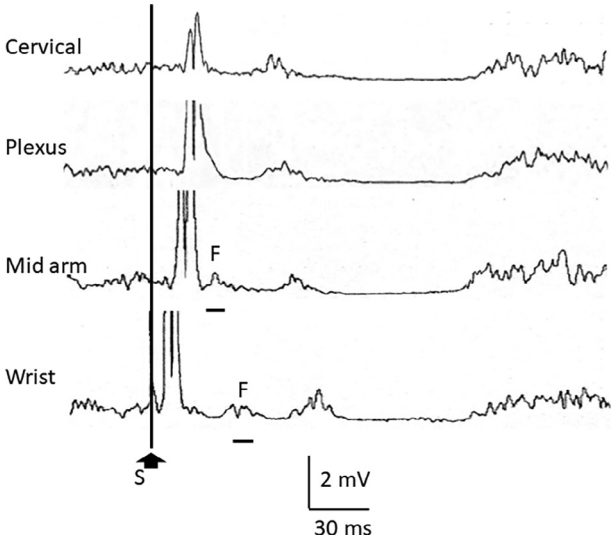

Fig. 5. Responses recorded from the right FDI during sustained voluntary contraction of mild intensity (50% of MVC) to magnetic stimuli applied to the cervical cord (first trace), brachial plexus (second trace) and midarm (third trace), as well as to electrical stimulation of the ulnar nerve at the wrist (fourth trace). Stimulus intensity was 200% RMT for CRMS. Note the progressive shortening of CMAP latency and lengthening of BISP, with maintenance of SP duration from proximal to distal stimulation. F = F wave.

stimulation in comparison to cervical stimulation (ANOVA; F[1,3] = 3.8; p = 0.024).

3.2.4. Results from additional tests

CRMS at 200% RMT did not induce any responses in the TA at rest. However, a well-defined silent period was present during contraction (Fig. 6), with a mean onset latency of 87.4 ms (SD = 9.4 ms) and a mean duration of 37.7 ms (SD = 10.1 ms). Same intensity stimuli at the plexus induced similar SPs with a mean onset latency of 92.1 ms (SD = 14.7 ms) and a mean duration of 29.8 ms

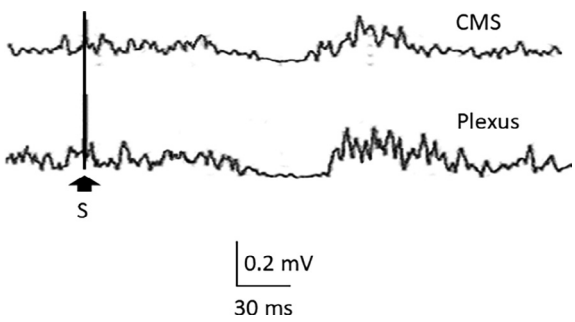

Fig. 6. Recording from the right tibialis anterior to cervical (upper trace) and plexus magnetic stimulation (lower trace) at an intensity of 300% RMT, during voluntary activation of the tibialis anterior at 75% of maximum voluntary contraction. Note the silent period appearing in this subject at an onset latency of 48 ms, without significant differences between the two stimulation sites.

(SD = 9.7 ms). Statistical comparison of these values indicated a significantly longer latency and shorter duration of the SP to plexus than to cervical magnetic stimulation (*t*-test; $p < 0.05$ for both comparisons).

Vibration induced a significant reduction of SP2 duration without affecting any other event (Fig. 7). The decrease was consistent in all 8 subjects, with a mean value of 26.3 (SD = 6.5) during vibration vs 61.6 (SD = 9.5) in the baseline. There were no significant changes in any other event.

PSTH was built from needle recording of low-level EMG activity in the FDI. Fig. 8A shows selected exemplary recordings from one of the two subjects at two intensities: below and above threshold for evoking a small response. The raw recordings show that there were consistent gaps in motor unit firing at both intensities, at latencies corresponding with the SPs, and a gathering of the same motor unit action potentials at times of the BISP and rebound events. A few other motor units, only sporadically recruited in the pre-stimulus epoch, appear also to contribute to the BISP and rebound. The consequence of both effects is shown with the histogram (Fig. 8B) where a pattern similar to the one obtained with surface recording is apparent. Peak latency of the largest bin corresponding to the BISP was 58.8 ms (SD = 7.2 ms), which was not different from the peak latency of the BISP recorded with surface electrodes at the same intensity and percentage of MVC (mean = 63.9 ms; SD = 10.7 ms).

4. Discussion

We have described in this manuscript the responses of the FDI to CRMS at rest and during sustained muscle contraction in healthy subjects, an experiment that would have been unreasonably painful if using electrical stimulation whether through needle or surface electrodes. As a mixed nerve stimulus, CRMS causes depolarization of the neural tissue and generates orthodromic and antidromic volleys in motor and sensory axons. While the characterization of responses at rest have already been the subject of previous publications, the characteristics of the events generated by CRMS in hand muscles during contraction have not been reported before.

4.1. Recordings at rest

The behaviour of the CMAP to CRMS was compatible with the reported concept of preferential side activation by the magnetic coil, as changing the coil face had a significant effect on the size of the CMAP (Ugawa et al., 1989; Matsumoto et al., 2013). Our results confirm that current flowing towards the spinal cord is most effective to depolarize the motor root/nerve at or near the foramina. This should be kept in mind when using CRMS for the assessment of CMCT, since there is also a substantial change in CMAP latency, depending on coil position. While this problem does not exist when measuring CMCT with the F wave method, the examiner should be aware that the two methods activate the nervous system in two different parts: the F wave does it in the motoneuron, while the CRMS does it at the root foramina. The combination of the two methods may be a useful strategy for the assessment of conduction time in the root segment (Inaba et al., 2002; Termuçin and Nurlu, 2011; Zheng et al., 2017). As expected, the increase of stimulus intensity led to progressively larger CMAPs, which maximum amplitude was near 100% of the CMAP to supramaximal intensity distal nerve stimulation (Matsumoto et al, 2010; Veltsista and Chroni, 2015).

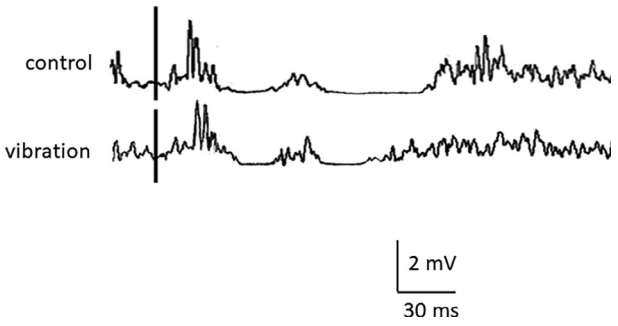

Fig. 7. Recordings from the right FDI to CRMS during sustained voluntary contraction of mild intensity (50% of MVC) when vibration was applied to the forearm (bottom trace) in comparison to a control condition, without vibration (top trace). Stimulation intensity was 200% RMT. Note the decreased duration of SP2 with vibration.

4.2. Recordings during muscle contraction

4.2.1. CMAp

As expected, the CMAP size increased with increasing stimulation intensity to CRMS, as more motor axons were recruited. Peak amplitude increased also with distal in comparison to proximal stimulation, together with the expected shortening in latency. Amplitude increase with distal stimulation may relate to better synchronization of the volley in nerve axons reaching the neuromuscular synapse because of shorter distance to the recording site, and better effectiveness of the induced current to activate the nerve closer to the tissue surface at the plexus, midarm and wrist than at the cervical site.

CMAP amplitude did not increase with increasing the strength of muscle contraction. This is coherent with the known fact that voluntary contraction does not significantly increase the number of axons activated by the stimulus. Instead, we found a barely significant decrease of CMAPs' peak amplitude at MVC. This could be due to various effects combined: 1. The increased level of background EMG activity may partially mask the real CMAP amplitude. 2. The increased number of voluntarily activated motor axons may reduce the likelihood of activation by the stimulus because of the refractory period (Borg, 1984, Burke et al., 2001), and 3. There can be a relative increase in threshold of the current needed to activate the axons because of contraction-induced axonal hyperpolarization (Milder et al., 2014).

4.2.2. SPs and BISP

The SP1, BISP and the SP2 have different physiological mechanisms implicated in their generation. However, their behaviour in our study is interrelated and, therefore, we consider the discussion of their characteristics in the same subchapter. There were no relevant stimulation intensity effects on SP1 or SP2. Both were ill-defined at low intensities but were of stable onset latency and duration once the stimulus reached a certain percentage above RMT, with no changes beyond that intensity. This suggests that some degree of synchronization in the axonal volleys and temporal summation at the target structures are necessary for the inhibitory effects to take place. SPs are known to occur in voluntarily contracting muscles with stimuli applied to mixed nerves (Ashby, 1995; Deuschl and Lücking, 1990). A characteristic phenomenon of the mnSP is the presence of an interrupting burst, termed BISP in this study. The BISP appeared at the end of the SP1 and before SP2. However, generation of the BISP is independent from generation of the SP1 or SP2, as it was recognizable at intensities lower than those needed to measure the SP1. The SPs and the BISPs observed to peripheral nerve stimulation are also different for stimuli applied exclusively to sensory fibres (Kofler et al., 2019a) or to a mixed nerve where the stimulus activates motor and sensory fibres simultaneously. In fact, the pattern of the events pro-

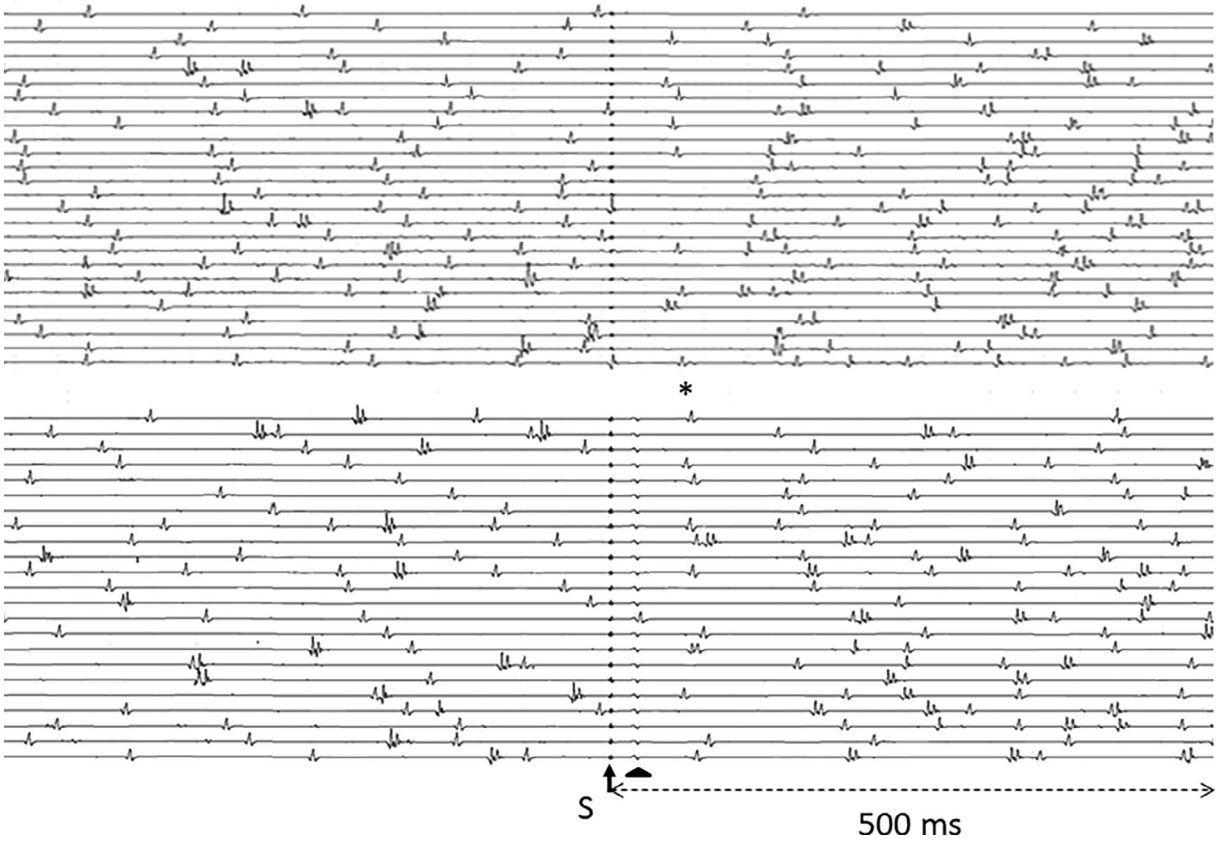

Fig. 8. Needle recordings of motor unit action potentials (A) and the peristimulus time histogram (B) representing the number of motor unit action potentials per 5 ms bins in 25 out of the 100 epochs of 500 ms recorded around the time of stimulus application (S) in one representative subject. The upper recording in A was done at low CRMS intensity, insufficient to recruit any CMAP, while the lower recording in A was done at higher CRMS intensity, which recruited a tiny response in every trace (arrowhead). Notice the motor unit action potential firing in the middle of an otherwise empty stretch, coinciding, respectively, with the BISP and the SP1 and SP2. Labels indicating where the corresponding events observed in the main study occurred are shown in B.

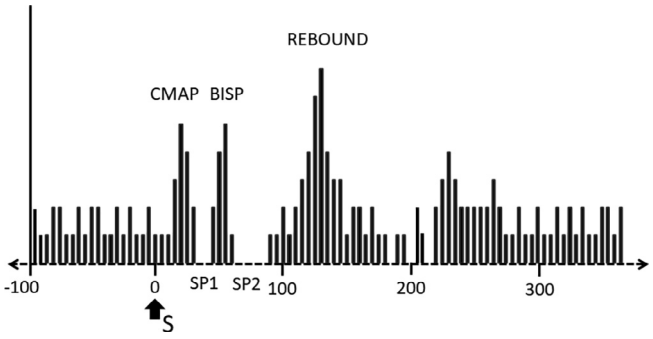

Fig. 8 (*continued*)

duced on contracting muscles by peripheral nerve stimuli should be characteristic for the site where the stimulus is applied and the type of fibres activated.

The SP1 originates likely because of events occurring in the motor fibres. The collision of the stimulus-generated antidromic volley with the axonal activity related to voluntary contraction would certainly lead to transient refractoriness in a number of axons, even if this will occur in a short segment after CRMS. The most relevant factor to account for the SP1, though, is likely the activation of the inhibitory Renshaw's cell by the first collateral, invaded by the antidromic impulses in axons that did not participate in the collision because they were not carrying impulses at the time of the stimulus. Renshaw's cell inhibitory effect is estimated to last about 40 ms (Stefanis and Jasper, 1964, Rothwell, 1994), which fits very well with the numbers obtained for the SP1 in our study (Tables 2–4).

All events other than the CMAP increased onset or peak latency when moving the stimulus from proximal to distal sites, indicating their origin in central loops (McLellan, 1973). The SP1 was no exception, although the onset latency would have shortened if measured just after the end of the CMAP. The F wave appeared with distal stimulation, dividing the SP1 in two parts. It is the last part of it (from the F wave to the BISP) which follows the rule of central origin. The F wave results from the rebound of antidromic volleys at the motoneuron, a relatively simple mechanism that differs from the more complex one leading to the BISP (although the possibility of an H reflex contributing to the response labelled here as F wave cannot be dismissed during sustained muscle contraction; Burke et al., 2016).

The BISP could have many sources. In studies of hand muscles reflexes to sensory stimuli, mixed nerve or cutaneous stimuli have been seen to generate long-loop reflex responses considered to have a *trans*-cortical pathway (Deuschl and Lücking, 1990; Valls-Solé and Deuschl, 2006; Lourenço et al., 2006). The same can be said for the E2 response to cutaneous stimuli (Chen et al., 1992) or the M2 response to mechanical stretch (Byblow et al., 2004). However, the BISP obtained in our study could also be generated by a mechanism related to a cascade of events partly described above for the generation of the SP1: the axons in which there was collision between descending and antidromic inputs were free from Renshaw's cell inhibition and, therefore, they were ready for firing again at the arrival of excitatory inputs involved in maintain-

ing the contraction level, a mechanism suggested also by Compta et al. (2006) to explain interrupting bursts found with subcortical stimulation of the corticospinal motor pathway.

The analysis of the psth helps understanding the generation of the BISP, as shown in Fig. 8: the motor unit action potential activated voluntarily showed a delay in its firing rate at the time of the stimulus and rebounded at a latency about 50–60 ms, compatible with the peak latency of the BISP reported in Tables 2–4. In summary, the data gathered in our study suggest that the BISP results from a transient increase of excitability in the motoneuron pool, which latency and amplitude would depend on the distance between the stimulus site and the motoneuron (the longest the distance the higher the number of axons undergoing collision), the strength of muscle contraction (the larger the number of axons containing inputs per unit of time the higher the possibilities of collision) and the intensity of the stimulus (the higher the number of motor axons activated the higher the number of motoneurons receiving Renshaw's inhibition).

The SP2 is likely generated by inhibitory inputs conveyed by sensory afferents, similar to the origin of the cutaneous silent period (CSP) described for the later part of the mnSP (Stetkarova et al., 2001; Kofler et al., 2019a). The CSP is considered a protective preattentional reflex response (Leis, 1994; Kofler et al. 2019a), which physiology has received much more attention than the study of the mnSP, probably because of clearer results and selectivity of the afferent input (for review, see Kofler et al., 2019a,b). A silent period compatible in latency with the SP2 was also obtained in our additional experiment, recording from the TA. It is known that a sensory input may cause inhibition beyond the local effect (Kofler et al., 2019a). The TA silent period was also obtained with plexus stimulation, which indicates the relatively widespread inhibitory effect of sensory afferents reaching interlimb propriospinal circuits (Faganel and Dimitrijevic, 1982).

The SP2 duration shortened with vibration and with increasing levels of muscle contraction. Such an effect has been reported for both types of conditioning stimuli, but with a lesser extent and consistency than those found in our study: Regarding muscle contraction, Kofler et al. (2019a) reported no effects at the recommended range of muscle contraction levels for examining the CSP (i.e., 10–60% of MVC); however, Serrao et al. (2001) found a significant shortening with high levels of muscle contraction. There are notable differences between studies that may explain why we found a more consistent effect, as we applied the stimulus to a proximal nerve site and activated all types of sensory afferents, while CSP studies were done with finger stimulation, limiting the afferent volley to the cutaneous sensory fibres innervating the finger. Regarding vibration, Binder et al. (2009) reported no changes in the mnSP, but Aydın et al. (2019) reported a barely significant reduction in duration of the CSP recorded from the abductor pollicis brevis to digital nerve stimulation. These results are in contrast with the consistent, largely significant, reduction of duration found in our study. It is possible that the excitatory influence of vibration (i.e., the tonic vibration reflex) contributes to the increase of EMG activity and counteracts the inhibitory inputs otherwise leading to the SP2.

4.3. Study limitations

Our study has several limitations which call for caution on the interpretation of the results discussed above. Magnetic stimulation is not focal enough to account for stimulation of a single root or nerve, and the surface recordings from the FDI are not selective enough to guarantee absence of contribution of volume conducted responses from activation of neighboring muscles. Activation of other muscles would be more likely with proximal than with distal stimulation and, therefore, comparison of responses to stimuli applied to different sites should be taken with caution. We do not know, though, up to what extent the contribution of other responses affects events other than the CMAP. We have only measured the events during contraction in the side where the responses were larger, disregarding the effects occurring in the other side. We have also chosen one stimulus intensity and one level of muscle contraction for the studies. Although we think that this was sufficiently informative, we cannot generalize our results to untested stimulus intensities and levels of muscle contraction. Finally, our outcome measures were limited to latency and amplitude of the events observed, although measuring the area of the rectified response is a more common procedure. We think, though, that measuring CMAP amplitude was fair, as it allowed for normalization of responses to the peak amplitude of the CMAP obtained with wrist stimulation of the ulnar nerve.

5. Conclusion

We have characterized the responses to CRMS in healthy subjects. For their most part, the CMAP and the SP1 can be explained by the effects of CRMS on motor fibres, while the SP2 is likely related to the effects on sensory afferents. BISP may be a product of simultaneous effects of CRMS on alpha motoneurons through antidromic impulses and long-loop reflexes elicited by the stimulus. Implication of spino-bulbo-spinal circuits must be considered for the generation of SP2 in distant muscles of both sides. This knowledge may be of clinical interest for testing the separate involvement of motor and sensory fibres in specific neurological disorders.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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