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RESEARCH ARTICLE

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Comparison of descending volleys evoked by monophasic and biphasic magnetic stimulation of the motor cortex in conscious humans

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Abstract The descending spinal volleys evoked by monophasic and biphasic magnetic stimulation of the motor cortex were recorded from a bipolar electrode inserted into the cervical epidural space of four conscious human subjects. The results suggest that both phases of the biphasic pulse are capable of activating descending motor output. The pattern of recruitment of descending activity depends on the intensity of the stimulus and the relative threshold of each volley to each direction of current flow.

Keywords Brain stimulation · Biphasic stimulation · Motor cortex · Descending volleys · Transcranial magnetic stimulation

Introduction

In a recent paper, Kammer et al. (2001) compared the efficiency of monophasic and biphasic stimulus waveforms for transcranial magnetic stimulation of the hand area of the motor cortex. They found that: (1) for a given amplitude of initial current, biphasic stimulation was more effective than monophasic stimulation, and (2) the most effective direction of the initial current was opposite for biphasic and monophasic stimulation. Thus, monophasic stimulation was most effective with a posterior-anterior (PA) induced current over the hand area, whereas biphasic stimulation was most efficient when the initial induced current was in the anterior-posterior (AP) direction and then reversed to a PA current. Indeed, with biphasic stimulation, the second phase of the biphasic stimulus seemed more effective than the first phase in stimulating both peripheral and central neurones. From their studies on isolated peripheral nerve, Maccabee et al. (1998) had postulated that this was because the reverse phase of the biphasic stimulus produced a larger charge transfer across the neuronal membrane than the initial phase. The advantage of the fast rising initial phase was more than offset by the slower rising, but longer lasting, reverse phase.

Effectively, these results suggest that threshold stimulation with a biphasic PA-AP induced pulse should behave similarly to a monophasic AP stimulus because the second phase of the biphasic stimulus would be the most effective part of the stimulus. Conversely, a biphasic AP-PA pulse might behave more similarly to a monophasic PA pulse.

The aim of the present experiments was to obtain more direct information about the nature of the structures activated by biphasic induced current in the brain. We have therefore taken advantage of the rare opportunity to record descending motor volleys directly from the cervical epidural space of conscious human patients with chronically implanted spinal electrodes. During routine testing of the continuity of the electrodes, we have been able in previous studies to characterise the pattern of recruitment of descending volleys evoked by monophasic PA and AP stimulation. Here we examine the volleys evoked by biphasic stimulation and compare them with the volleys evoked in the same individuals by monophasic stimulation.

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Materials and methods

Corticospinal volleys evoked by transcranial magnetic stimulation of the motor cortex were recorded from the high cervical cord in four patients with no abnormality of the central nervous system (mean age 57±19 years). The patients had a spinal cord stimulator implanted for treatment of intractable dorsolumbar pain. The electrode (Model Quad 3487A Medtronic, Minneapolis) was implanted percutaneously in the epidural space at the C1–C2 level, and recordings of descending activity made 2–3 days after implantation during the trial screening period when the electrode connections were externalised. The subjects gave informed consent to the study, which was performed with the approval of the appropriate Institutional Ethics Committee.

Recordings were made simultaneously from the epidural electrode and from the first dorsal interosseous muscle (FDI) of the left hand. Epidural potentials were recorded between the most proximal and most distal of the four electrode contacts on each implant. These had a surface area of 2.54 mm^2 and were 30 mm apart. The distal contact was connected to the reference input of the amplifier. Surface EMGs were obtained via two 9-mm-diameter Ag-AgCl electrodes with the active electrode over the motor point of the muscle and the reference on the metacarpophalangeal joint of the index finger. EMGs and the corticospinal volleys were amplified and filtered (bandwidth 3 Hz to 3 kHz) by D150 amplifiers (Digitimer, Welwyn Garden City, Herts., UK). Data were collected on computer and stored for later analysis using a CED 1401 A-D converter (Cambridge Electronic Design, Cambridge, UK). Active motor threshold (AMT) was defined as the minimum stimulus intensity that produced a liminal motor evoked response (about 150–200 µV in 50% of trials) during isometric contraction of the tested muscle at about 20% maximum. A constant level of voluntary contraction was maintained with reference to an oscilloscope display of EMG in front of the subject. Auditory feedback of the EMG activity was also provided. Resting motor threshold (RMT) was defined as the minimum stimulus intensity that produced a liminal motor evoked response (about 150–200 µV in 50% of trials) while recording at rest. RMT and AMT were determined separately for the different monophasic and biphasic stimulation for each of the different stimulation conditions separately.

Latency and amplitude of EMG responses were evaluated on mean responses to ten stimuli. The latency of EMG response was measured on its onset and the amplitude was measured peak-topeak.

Monophasic magnetic stimulation

Monophasic magnetic stimulation was performed with a high power Magstim 200 (Magstim Co., Whitland, Dyfed, UK). A figure-of-eight coil with external loop diameters of 9 cm was held over the right motor cortex at the optimum scalp position to elicit motor responses in the contralateral FDI using two different orientations over the motor strip.

LM magnetic stimulation was used to identify the latency of the earliest (D-wave) descending volley (Di Lazzaro et al. 1998). The responses to ten stimuli at an intensity of AMT and 150% AMT (subjects 1 and 4), at an intensity of 150% AMT (subject 2) and at RMT intensity (subject 3) were averaged at rest in all subjects and also during maximum voluntary contraction of FDI in subjects 1 and 4. PA magnetic stimulation of the motor cortex was used to identify the latency of the later (I-waves) descending volleys (Di Lazzaro et al. 1998). The responses to ten stimuli were averaged both at rest and during maximum voluntary contraction in subjects 1, 2 and 4 and at rest only in subject 3. PA stimulation was performed at an intensity of AMT, 110% AMT and 150% AMT in subjects 1 and 4, at an intensity of 150% AMT in subject 2 and at RMT intensity in subject 3. In subjects 1, 3 and 4 we also performed AP magnetic stimulation at rest and during voluntary contraction at an intensity of AMT and 150% AMT in subjects 1 and 4 and at RMT intensity at rest in subject 3.

Biphasic magnetic stimulation

Biphasic magnetic stimulation was performed with a Magstim Super Rapid (Magstim Co., Whitland, Dyfed, UK). This stimulator produces a biphasic pulse. A figure-of-eight coil with external loop diameters of 9 cm was held over the right motor cortex at the optimum scalp position to elicit motor responses in the contralateral FDI. The current profile induced in a coil by the Super Rapid Magnetic stimulator is biphasic, with a period of 331 µs. The direction of the current induced in the brain was posterior-anterior followed by anterior-posterior (PA-AP).

Stimulation was performed at increasing stimulus intensities starting from AMT to 150% AMT in subjects 1 and 4 and to 200% AMT in subject 2. In subject 3, stimulation was performed only at 120% RMT intensity. The responses to ten stimuli were averaged both at rest and during maximum voluntary contraction in subjects 1, 2 and 4 and at rest only in subject 3.

In subjects 1 and 4 we also evaluated the effects of reversing the direction of the phases of the biphasic stimulus (AP-PA). Stimulation was performed at increasing stimulus intensities starting from AMT to 150% AMT, both at rest and during maximum voluntary contraction.

We did not explore the effect of biphasic stimulation with other coil orientations such as that inducing lateromedial current in the brain followed by mediolateral current because the time to study patients was limited.

The latency of each component of the descending volley was measured to its peak because the precise onset was often difficult to define for all but the first component. Amplitudes were measured from the peak to the next trough in order to minimise distortions due to stimulus artefact. Only consistent deflections with a mean amplitude over ten responses of >2 µV were analysed.

Results

Recordings are shown in Figs. 1, 2, 3, and 4. Threshold and latency values are summarised in Table 1.

Monophasic stimulation

LM stimulation

LM magnetic stimulation evoked the shortest latency volley in all subjects. As we have argued in previous papers (Di Lazzaro et al. 1998), it is probably equivalent to the D-wave described by Patton and Amassian (1954). In subjects 1 and 4, maximum voluntary contraction had no effect on the amplitude of this wave. We assume that later waves are I-waves, numbered in order of their appearance.

PA stimulation

Only subjects 1 and 4 were examined at a range of intensities. The pattern of recruitment of descending activity was similar to that described previously (Di Lazzaro et al. 1998). The lowest threshold volley recruited an I1-wave that had a latency 1.4 ms longer than the LM D-wave. This volley increased in size, and was followed by later volleys as the intensity of stimulation was increased. Maximum voluntary contraction increased the amplitude of the I-waves (e.g., at 150% AMT stimulus

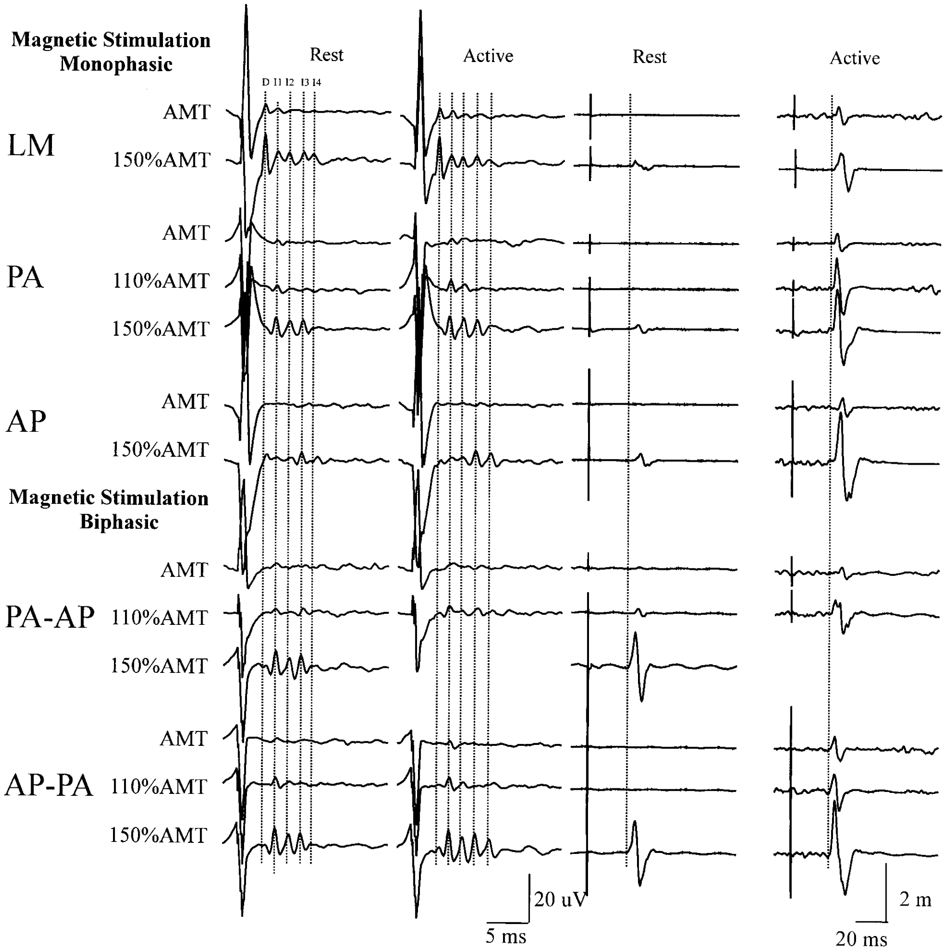

Fig. 1 Descending volleys evoked by LM monophasic magnetic stimulation, PA monophasic magnetic stimulation, AP monophasic magnetic stimulation and bipolar magnetic stimulation at increasing stimulus intensities at rest and during maximum voluntary contraction of the tested muscle in subject 1. Epidural volleys are shown *on the left* and EMG responses from the FDI are shown on a longer time scale *on the right*. The latencies of the D- and I-waves evoked by monophasic LM and PA magnetic stimulation are indicated by *vertical dotted lines*. LM stimulation evokes a clear D-wave; PA stimulation evokes only I-waves, recruited in order I1, I2, I3 as the intensity is increased. AP stimulation tends to evoke later I-waves at threshold, and even at 150% threshold the I1-wave is not very clear. At threshold intensity, bipolar PA-AP magnetic stimulation evokes an I1-wave that has the same latency as the I1-wave after monophasic PA stimulation at the same intensity. At higher intensities, the recruitment of additional waves appears more similar to that after monophasic AP stimulation. At 110% AMT, later I-waves (around I3 latency) are more prominent than after PA stimulation and at 150% AMT a late D-wave is recruited that has the same latency as that after AP stimulation. Reversing the direction of the current of the two phases of the biphasic stimulus (AP-PA) evokes volleys similar to those evoked by monophasic PA stimulation. An I1-wave is recruited at lowest intensity; however, the latency of this I1-wave has a latency 0.3 ms longer than the I1-wave evoked by monophasic PA stimulation. At the highest intensity used the latency of the I1 shortens and a late D-wave is recruited that has the same latency as that after monophasic AP stimulation

intensity there was an increase of about 23% in subject 1 and of about 26% in subject 4 compared with the rest). Subject 2 was studied only at 150% AMT. Stimulation evoked D- and I-waves that had the same latencies as those seen with 150% LM stimulation. Subject 3 was studied only at RMT intensity. Stimulation evoked three waves, the earliest of which was an I1-wave with a latency that was 1.3 ms longer than the D-wave evoked by LM stimulation.

AP stimulation

This was performed in subjects 1, 3 and 4. The order of recruitment of the volleys was not studied in detail, but it can be noted in comparison with PA stimulation that in subject 1, late I-waves were recruited in preference to I1-waves, and in subject 4, a D-wave was recruited rather than I-waves. As reported previously (Di Lazzaro et al. 2001), the latency of the volleys was often slightly longer than that after PA stimulation. Thus, the D-wave occurred about 0.3 ms later than the LM D-wave in all three subjects, and in subjects 1 and 3, the I1 wave was slightly later than the PA I1-wave. In subject 1, the I-waves were facilitated by about 70% during maximum voluntary contraction. In subject 4, the D-wave at AMT was facilitated by voluntary activation.

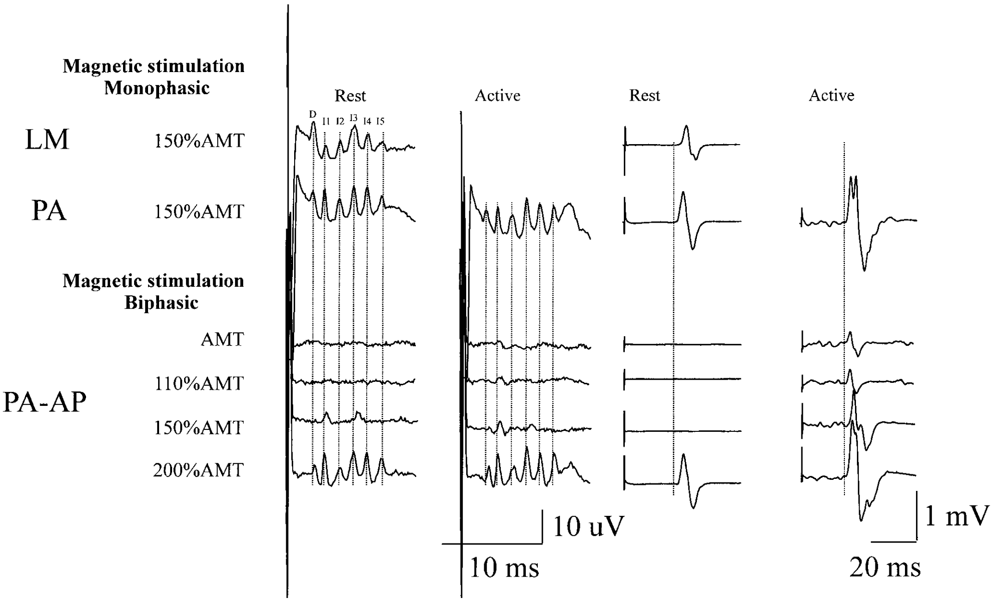

Fig. 2 Descending volleys evoked by LM monophasic magnetic stimulation, PA monophasic magnetic stimulation and bipolar magnetic stimulation at increasing stimulus intensities at rest and during maximum voluntary contraction of the tested muscle in subject 2. Epidural volleys are shown *on the left* and EMG responses from the FDI are shown on a longer time scale *on the right*. The latencies of the D- and I-waves evoked by monophasic LM and PA magnetic stimulation are indicated by *vertical dotted lines*. At threshold intensity, bipolar magnetic stimulation evokes a delayed epidural volley during maximum voluntary contraction of the tested muscle that has a latency 0.2 ms longer than the I1-wave evoked by monophasic PA magnetic stimulation. No epidural volley is recorded at rest. At a stimulus intensity corresponding to 150% AMT, this volley is recognisable even at rest and it is followed by a delayed I3-wave. At 200% AMT, the I-wave latency becomes the same as with PA stimulation, but a D-wave is recruited that has a longer latency than the D-wave from PA or LM stimulation

Table 1 Threshold and latencies for each subject studied. Latency measurements are made at threshold for each volley (*ND* not examined, – no response at this latency)

	Stimulus type	Subject 1	Subject 2	Subject 3	Subject 4
Monophasic stimulation					
Threshold	LM	32	22	43[a]	40
(% maximum stimulator output)	PA	30	23	50[a]	37
	AP	35	ND	56[a]	47
D-wave latency (ms)	LM	2.8	2.5	2.4	2.6
	PA	–	2.5	–	2.6
	AP	3.2	ND	2.7	2.9
I1-wave latency (ms)	PA	4.3	3.8	3.7	4.0
	AP	4.6	ND	3.9	4.3
Biphasic stimulation					
Threshold	PA-AP	52	33	60[a]	55
(% maximum stimulator output)	AP-PA	43	ND	ND	45
D-wave latency (ms)	PA-AP	3.2	2.7	–	2.9
	AP-PA	–	ND	ND	2.9
I1-wave latency (ms)	PA-AP	4.3	4	3.9	4.3
	AP-PA	4.6	ND	ND	4.3

[a] In subject 3, threshold values are for RMT, whereas threshold is given for AMT in all other subjects

Biphasic stimulation

In view of the previous data of Maccabee et al. (1998) and Kammer et al. (2001), we had expected that PA-AP stimulation might recruit volleys such as monophasic AP stimulation, whereas AP-PA stimulation might behave like monophasic PA stimulation. This was often the case, but very often a mixture of effects was observed. Only subjects 1 and 4 were examined at a range of intensities and with all forms of stimulation.

PA-AP stimulation

In subject 1, stimulation at AMT recruited an I1-wave that had the same latency as the I1-wave after monophasic PA stimulation at the same intensity. However, at higher intensities, the recruitment of additional waves appeared more similar to that after monophasic AP stimulation. Thus, at 110% AMT, later I-waves (around I3 latency) were more prominent than after PA stimulation and at 150% AMT a late D-wave was recruited that had

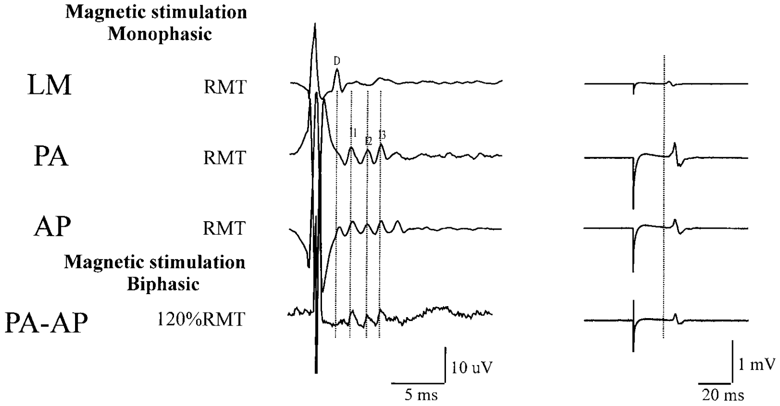

Fig. 3 Descending volleys evoked by LM monophasic magnetic stimulation, PA monophasic magnetic stimulation, AP monophasic magnetic stimulation and bipolar magnetic stimulation at RMT intensity at rest in subject 3. Epidural volleys are shown *on the left* and EMG responses from the FDI are shown on a longer time scale *on the right*. The latencies of the D- and I-waves evoked by monophasic LM and PA magnetic stimulation are indicated by *vertical dotted lines*. LM stimulation evokes a clear D-wave; PA stimulation evokes only three I-waves; AP stimulation evokes slightly delayed D- and I1-waves and three later I-waves. Bipolar PA-AP magnetic stimulation evokes I-waves that are later than those after PA stimulation and more similar to I-waves recruited by monophasic AP stimulation

the same latency as that after AP stimulation. Subject 2 had not been studied with AP stimulation, but the latency of the I1- and I3-waves was later than those evoked by PA stimulation at 110% and 150% AMT. At 200% AMT, the I-wave latency became the same as with PA stimulation, but a D-wave was recruited that had a longer latency than the D-wave from PA or LM stimulation.

Subject 3 was only studied at a single intensity of PA-AP stimulation. As with the other subjects, the latency of the I-waves was later than that after PA stimulation and more similar to I-waves recruited by AP stimulation. In subject 4, stimulation at AMT recruited an I1-wave and a D-wave that had a later onset than that seen after high intensity PA stimulation. At 150% AMT, the I-wave latency was the same as for PA stimulation, but the D-wave had the same latency as AP stimulation.

AP-PA stimulation

This type of stimulation was performed only in subjects 1 and 4. AMT was lower than AMT to PA-AP stimulation. In both subjects, the pattern of recruitment of D- and I-waves at increasing stimulus intensities resembled that after monophasic PA stimulation more than after AP stimulation. Thus, in subject 1, an I1-wave was recruited at lowest intensity, then the I2- and the I3-waves. The I3-wave was never more prominent than the I1-wave as seen after AP stimulation. Similarly, in subject 4, an I1-wave was recruited before the D-wave, whereas the D-wave was recruited first after AP stimulation. However, in subject 4, the latency of the both the D- and I1-waves, even at 150% AMT, was 0.3 ms longer than after PA stimulation. In subject 1, the latency of the I1-wave shortened by about 0.3 ms as the intensity was increased from 100% to 150% AMT.

Observations on the EMG responses

There are two points of interest about the EMG responses. First, the relationship between descending volley and amplitude of response could be quite different for different forms of stimulation even in the same subject. For example, the EMG response recorded at rest in subject 1 is approximately the same amplitude at 150% AMT for AP stimulation and 110% AMT PA-AP stimulation; yet the descending volleys are much larger for the former than the latter. This is presumably because the volleys recorded in the spinal cord may not always be destined for the FDI muscle that we recorded. The implication is that different forms of stimulation can activate different proportions of fibres destined for FDI. Second, the latency of the EMG responses at AMT sometimes did not correspond to the latency of the earliest descending volley. For example, in subject 1, stimulation at AMT during contraction appeared to evoke an I1-wave for both PA and PA-AP stimulation; yet the EMG response was about 3 ms later after the latter type of stimulus. Again, this is best explained by apparently similar volleys recruited by different forms of stimulation which may actually be destined for different sets of muscles.

Discussion

The present experiments confirm our previous results about how different directions of monophasic stimulation affect the order of recruitment of D- and I-waves. LM stimulation recruits D-waves at low intensities; PA stimulation recruits I1-waves preferentially, with later I-waves appearing in sequence at higher intensities and D-waves at very high intensities; AP stimulation recruits D- and I-waves in a different order, and sometimes with slightly

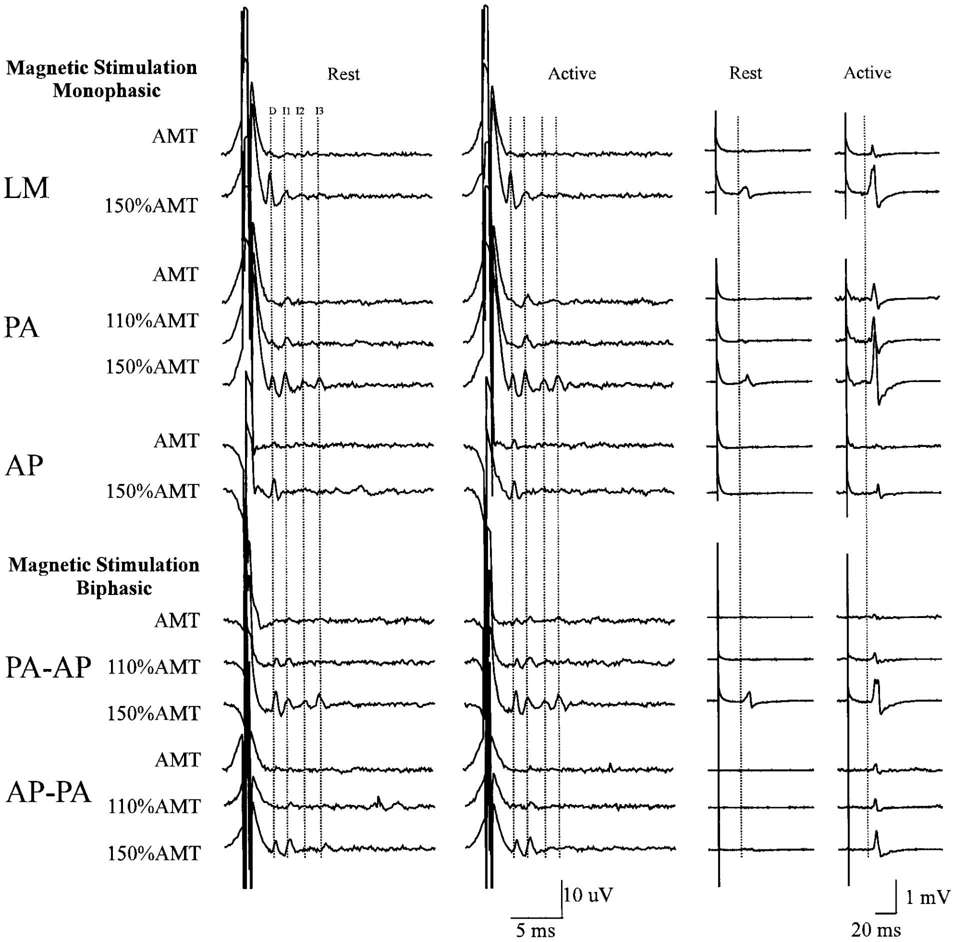

Fig. 4 Descending volleys evoked by LM monophasic magnetic stimulation, PA monophasic magnetic stimulation, AP monophasic magnetic stimulation and bipolar magnetic stimulation at increasing stimulus intensities at rest and during maximum voluntary contraction of the tested muscle in subject 4. Epidural volleys are shown *on the left* and EMG responses from the FDI are shown on a longer time scale *on the right*. The latencies of the D- and I-waves evoked by monophasic LM and PA magnetic stimulation are indicated by *vertical dotted lines*. LM stimulation evokes a clear D-wave; PA stimulation evokes I-waves and at the highest stimulus intensity used a clear D-wave. AP stimulation evokes a delayed D-wave. At threshold intensity, bipolar magnetic stimulation recruits an I1-wave and a D-wave that have a later onset than that seen after high intensity PA stimulation. At 150% AMT, the I-wave latency is the same as for PA stimulation, but the D-wave has the same latency as AP stimulation. Reversing the direction of the current of the two phases of the biphasic stimulus (AP-PA), an I1-wave is recruited before the D-wave and even at 150% AMT the latency of both the D- and I1-waves is 0.3 ms longer than after PA stimulation

different latencies than PA stimulation, often with a preference for the I3-wave. If a D-wave is recruited, it has a later onset than the LM D-wave, consistent with activation nearer the cell body of the pyramidal neurones than the conventional D-wave (Di Lazzaro et al. 2001). Indeed, in subject 4, this D-wave was facilitated by voluntary contraction. The results also confirm the observation of Kammer et al. (2001) that biphasic stimulation has a lower threshold when the initial phase of induced current flows in the anterior-posterior direction. This is opposite to the preferred direction for monophasic stimulation of the hand area.

The new feature of the present data concerns the descending volleys evoked by biphasic stimulation. They illustrate the practical application to the cortex of the arguments that Maccabee et al. (1998) developed on isolated nerve axons. They showed that the reverse phase of a hyperpolarizing-depolarising biphasic pulse was more effective in stimulating an axon than a monophasic depolarising pulse of the same peak amplitude. From the point of view of motor cortex stimulation, this means that AP-PA pulses should behave like a PA pulse, with the responses delayed by about 0.1 ms to account for the duration of the biphasic waveform. The data were compatible with this. In subject 1, the recruitment of descending activity by AP-PA stimulation was almost identical, although slightly later than that after PA stimulation. In subject 4, low intensities of AP-PA stimulation appeared to recruit an I1-wave as after PA stimulation. However, the fact that the latency of the D-wave was 0.3 ms longer than after PA stimulation suggested that the AP phase of the biphasic pulse could also stimulate the cortex, presumably because D-wave threshold in this subject was so much lower with monophasic AP than PA stimulation.

It is more difficult to predict the effect of PA-AP stimulation. The reason is that in most subjects the threshold for monophasic AP stimulation is higher than for monophasic PA stimulation. Thus, even if the AP phase of a PA-AP pulse is more effective than a monophasic AP pulse, it is also possible that the initial PA phase wins the race to activate the cortex because of its lower threshold. The results confirmed that in practice a mixture of effects could occur. In subjects 2 and 3, PA-AP stimulation seemed to recruit I-waves like monophasic AP stimulation, whereas in subjects 1 and 4, the lowest threshold volleys seemed to resemble those evoked by PA stimulation, but at higher intensities volleys consistent with activation by the AP phase of the pulse were seen. We believe this combination of results is consistent with the idea that both phases of the pulse activate cortical neurones, and that the mixture that is observed depends on the relative threshold of elements to PA and AP stimulation. Even though the second phase of the biphasic pulse is the more effective part of the stimulus, it does not always win in the race to activate cortical elements.

In conclusion, biphasic stimulus pulses produce a more complex pattern of cortical activation than monophasic pulses. Both phases of the stimulus pulse can activate descending pathways, but the precise combination of elements activated by AP and PA directions depends on their relative threshold and the relative amplitude of the AP and PA phases.

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