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Motor thresholds in humans: a transcranial magnetic stimulation study comparing different pulse waveforms, current directions and stimulator types

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Abstract

Objectives: To evaluate the stimulation effectiveness of different magnetic stimulator devices with respect to pulse waveform and current direction in the motor cortex.

Methods: In 8 normal subjects we determined motor thresholds of transcranial magnetic stimulation in a small hand muscle. We used focal figure-of-eight coils of 3 common stimulators (Dantec Magpro, Magstim 200 and Magstim Rapid) and systematically varied current direction (postero-anterior versus antero-posterior, perpendicular to the central sulcus) as well as pulse waveform (monophasic versus biphasic). The coil position was kept constant with a stereotactic positioning device.

Results: Motor thresholds varied consistently with changing stimulus parameters, despite substantial interindividual variability. By normalizing the values with respect to the square root of the energy of the capacitors in the different stimulators, we found a homogeneous pattern of threshold variations. The normalized Magstim threshold values were consistently higher than the normalized Dantec thresholds by a factor of 1.3. For both stimulator types the monophasic pulse was more effective if the current passed the motor cortex in a postero-anterior direction rather than antero-posterior. In contrast, the biphasic pulse was weaker with the first upstroke in the postero-anterior direction. We calculated mean factors for transforming the intensity values of a particular configuration into that of another configuration by normalizing the different threshold values of each individual subject to his lowest threshold value.

Conclusions: Our transformation factors allow us to compare stimulation intensities from studies using different devices and pulse forms. The effectiveness of stimulation as a function of waveform and current direction follows the same pattern as in a peripheral nerve preparation (J Physiol (Lond) 513 (1998) 571).

Keywords: Human motor cortex; Thresholds; Current direction; Pulse waveform; Stimulation effectiveness; Transformation factors

1. Introduction

Cortical excitability varies between subjects. In the case of transcranial magnetic stimulation (TMS), it depends on the thickness of the skull as well as on cortical network properties controlled by neuromodulators (Ziemann et al., 1998b). Therefore, it is common in studies using TMS to normalize stimulus intensities with respect to individual excitability. To determine individual excitability, most of the studies measured thresholds in the motor cortex because the motor cortex is the only region where the excitatory effect has a directly measurable physiological effect in the form of compound muscle action potentials (CMAP) of twitching muscles.

The effect of TMS on cortical neurons depends on the geometry and orientation of the induced electric field (Amassian et al., 1992), as well as on the current pulse waveform delivered by the stimulator (Brasil-Neto et al., 1992). Two different classes of waveforms can be distinguished: biphasic (or polyphasic) and monophasic (Fig. 1). The biphasic or polyphasic waveform results from the current pulse applied to the coil followed by an oscillation due to the self-induction properties of the coil (Cadwell, 1990). The pulse can be terminated after one full cycle of the oscillation (biphasic) or after several oscillation cycles (polyphasic). To generate a monophasic waveform the self-induction of the coil has to be damped with a shunting diode and a power resistor (Barker et al., 1987).

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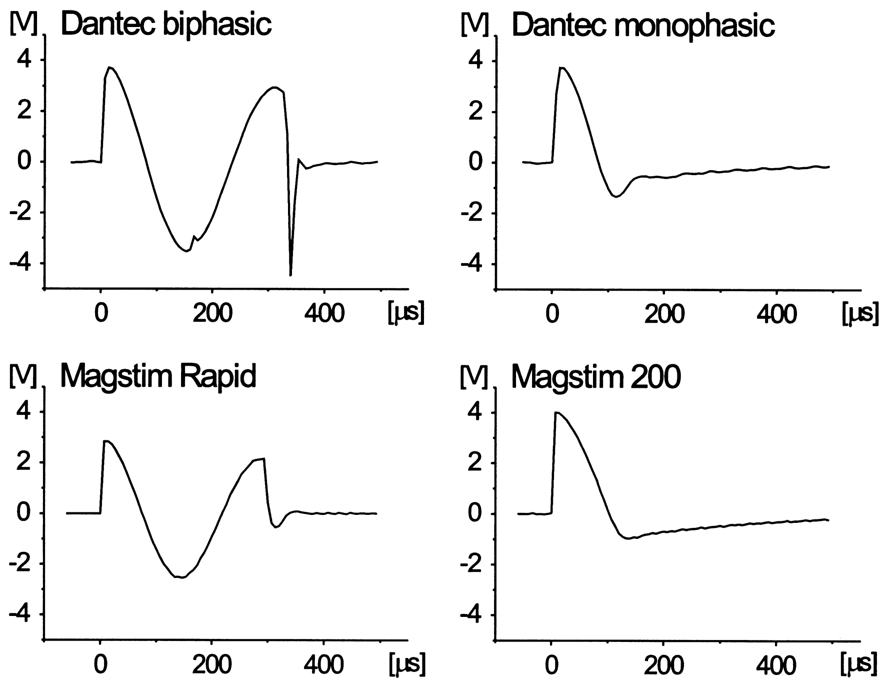

Fig. 1. Pulse waveforms used in the experiment, measured at maximal output intensity with a simple induction coil (one loop) at a distance of 15 mm from the windings. The voltages measured are proportional to the induced tissue currents in the brain. The first rising phases of the Dantec configurations are identical in amplitude. In contrast, the peak amplitude of the Magstim Rapid is only about 71% of that of the Magstim 200. Due to the different geometries of the figure-of-8 coils (the Dantec coil is slightly angulated, the Magstim coil is flat) the amplitudes of the Dantec and Magstim are not directly comparable with this measurement. The amplitude ratios of the first positive and negative phases are 100/95 and 100/36 for the Dantec pulses, and 100/90 and 100/25 for the Magstim pulses.

In the past, many of the single pulse studies on the motor cortex were performed with monophasic waveforms, in particular those studies examining motor thresholds (Mills and Nithi, 1997; Rossini et al., 1992; Triggs et al., 1994). However, a new generation of stimulators generates mainly biphasic pulses. These stimulators are optimized to provide repetitive stimulation trains with frequencies of up to 50 Hz. The purpose of these trains is to modulate the excitability of cortical areas for scientific and therapeutic reasons, primarily in psychiatric disorders such as major depression (George et al., 1995; Pascual-Leone et al., 1996). Furthermore, repetitive magnetic stimulation makes it possible to explore the function of the motor cortex in more detail (Pascual-Leone et al., 1994; Topka et al., 1999). Repetitive stimulators generate biphasic waveforms, because much of the applied energy is restored in the capacitor during an oscillation period, reducing the amount of recharge energy between the pulses. In applications using biphasic pulses the threshold measurements in the motor cortex are performed with the biphasic waveform as well.

Since a lot of laboratories actually use both monophasic and biphasic waveforms side by side, depending on the ultimate goal of the application, we wondered whether the efficiency of the pulse waveforms could be compared quantitatively. We also set out to compare the effectiveness of stimulators from two different manufacturers: Dantec and Magstim. And finally, we were interested in the effects of different current directions in the brain. Using the standard focal figure-of-eight coils, our study revealed a consistent pattern of threshold differences between stimulator systems. On the basis of our findings, we were able to calculate ratios of stimulation intensity levels, which allow one to estimate the relative power of a given configuration with respect to another one.

2. Methods

2.1. Subjects

Eight subjects (age 22–36 years, 4 female, 4 male) were investigated. They were all in good health and had no history of neurological disorders. The experiments were approved by the Ethics Committee of the Medical Faculty, University of Tübingen. Written informed consent was obtained.

2.2. Experimental set-up

CMAP were recorded with surface electrodes taped over the belly and the tendon of the right abductor pollicis brevis muscle. Signals were filtered and amplified with a conventional electromyograph (Dantec Keypoint portable, Skovlunde, Denmark), using a bandpass of 20–20 000 Hz, a sweep duration of 5 ms/div and a display gain of 50 μV/div.

Subjects were given auditory feedback from the electromyograph to ensure that the recorded muscles remained at rest.

Three different magnetic stimulators with focal figure-of-eight coils were used: Dantec Magpro (Skovlunde, Denmark), Magstim 200 (Whitland, Dyfed, UK) and Magstim Rapid in a configuration with two booster modules. It is important to note that the number of booster modules only determines the maximal frequency of stimulation trains, not the energy of the individual pulse (Reza Jalinous, pers. commun.). The standard figure-of-eight focal coil from Dantec (MC-B70) is angled 140°; the two windings each have a diameter of 24–96 mm, and a mean diameter of 60 mm (measured by X-ray). The Magstim figure-of-eight coil (P/N 9790) is not angled; the two windings each have a diameter of 56–91 mm, and a mean diameter of 74 mm. The following stimulation parameters were varied: stimulation coil (Dantec/Magstim), current waveform (biphasic/monophasic) and current direction in the brain (postero-anterior/antero-posterior with respect to the first phase). All 8 possible configurations were investigated in each subject (Table 1). In the case of the Dantec coil all 4 different configurations could be measured without changing the coil position by simply switching the current direction and the waveform at the stimulator device. The Magstim coil was rotated about 180° so that the handle pointed to the front or to the back in order to change the current direction. The waveform was changed by stimulating with the Magstim Rapid (biphasic) and the Magstim 200 (monophasic), respectively.

2.3. Current directions

We measured the current directions in the coils by means of an induction loop (Fig. 1). In the Dantec coil the first rising phase of the current pulse is directed from the handle towards the front end of the coil when the ‘normal’ current direction is chosen. This current direction in the coil is depicted by two arrows over the junction of the two coil loops. In the Magstim coil the first rising phase is always directed from the front end of the coil towards the handle, both in the case of the monophasic pulse (Magstim 200) and the biphasic pulse (Magstim Rapid). The arrows over the junction point from the handle to a minus symbol at the front. These arrows do not indicate the current direction in the coil, but rather the evoked current flow in the brain. The minus symbol represents a virtual cathode in the brain. This was confirmed by the manufacturer (Reza Jalinous, pers. commun.). For the sake of clarity, current directions in the coil and the brain are given with respect to the handle orientation in Table 1.

2.4. Maintenance of the coil position

Subjects lay in a supine position in a comfortable chair. The coil was fixed on a tripod. To maintain the position of the coil with respect to the head we used a positioning device described in detail elsewhere (Kammer et al., unpublished data). Briefly, the position of the head was monitored online by means of a mechanical digitizing arm (MicroScribe 3DX 6DOF, Immersion Corp., San Jose, CA, USA) attached to the head with a headband. A head-based coordinate system was established at the beginning of each session by means of anatomical landmarks. The position of the coil was monitored simultaneously with a second arm. Custom-made software running on a PC continuously calculated the relative position of the coil with respect to the head-based coordinate system. To maintain the position defined at the beginning of the experiment (see below) the subjects observed a visual feedback of their own head position on a monitor, where two squares were displayed. The square referring to the coil was stationary, and the other one displayed the head position with respect to the coil position. Translation of the head in the frontal plane translated the square and rotation on a sagittal axis rotated the square. Translation along the sagittal axis shrank or enlarged the square. Rotations on the transversal or axial axis deformed the square into a trapezium to represent the 3D projection of a square rotated in space. With some practice the subjects were able to control the position of the head throughout several threshold measurements. Breaks were allowed as

Table 1
Magnetic stimulators, pulse waveforms, and current directions used[a]

Stimulator	Pulse waveform	Energy W (J)	$\sqrt{W}$	Current direction switch	Coil handle	Current direction (midline of coil)	Current direction (brain)
Dantec Magpro	Biphasic	300	17.32	Normal	Front	Handle-coil	Postero-anterior
Dantec Magpro	Biphasic			Reversed	Front	Coil-handle	Antero-posterior
Dantec Magpro	Monophasic	300	17.32	Normal	Front	Handle-coil	Postero-anterior
Dantec Magpro	Monophasic			Reversed	Front	Coil-handle	Antero-posterior
Magstim Rapid	Biphasic	252	15.87	-	Back	Coil-handle	Postero-anterior
Magstim Rapid	Biphasic			-	Front	Coil-handle	Antero-posterior
Magstim 200	Monophasic	720	26.83	-	Back	Coil-handle	Postero-anterior
Magstim 200	Monophasic			-	Front	Coil-handle	Antero-posterior

[a] W indicates the maximal energy stored in the capacitor. Values were provided by the manufacturers. Current directions are indicated in the technical convention from plus to minus. In the case of biphasic waveforms the current direction of the first phase is given. Please notice that the coils were rotated about 30–45° from a parasagittal plane in order to direct the current perpendicular to the central sulcus. To simplify the nomenclature the current directions refer to this individually adjusted rotated direction.

needed after a threshold measurement. When the measurements were resumed the position of the coil was reconstructed with a maximum deviation of 2 mm.

2.5. Threshold measurements

Threshold measurements of the 8 configurations were carried out in a single session lasting about 7 h or in two separate sessions on two different days. The order in which the different measurements were taken was randomized. The coil was placed tangentially over the skull at the region of the left motor cortex. Using a suprathreshold TMS pulse a position was carefully determined with the maximal CMAP response (‘hot spot’). To obtain the maximal response the handle of the coil was rotated clockwise about 30–45° in the tangential plane, presumably perpendicular to the central sulcus (Brasil-Neto et al., 1992; Mills et al., 1992). In the case of the Dantec coil the optimal position was determined in the normal biphasic mode (current in the brain postero-anterior), irrespective of the randomized measuring sequence; this position was used for all 4 different modes. The position of the Magstim coil was readjusted for the modes handle front and handle back using the Magstim 200, irrespective of the randomized measuring sequence. Rotation in the tangential plane was determined in the first of the randomized coil blocks and then maintained in the second and third blocks, with a 180° flip between Magstim front and back. For the sake of consistency, current directions in the brain will always be referred to as ‘postero-anterior’ or ‘antero-posterior’, irrespective of the angular rotation of the coil.

We have defined a peak to peak amplitude of at least 50 μV CMAP as the motor threshold criterion in the relaxed muscle. This level has been used previously (Wilson et al., 1995; Ziemann et al., 1996). It lies between the lowest threshold criterion (20 μV) defined by Mills and Nithi (1997) and the higher one (100 μV) suggested by Rossini et al. (1994). We stimulated 10 times at each stimulator output level. The stimulation frequency was 0.2 Hz or less. Following Mills and Nithi (1997) we determined an upper threshold level of 10/10 CMAPs of >50 μV and a lower threshold level of 0/10 CMAPs of >50 μV. To make sure that we had really reached the upper and lower thresholds we required at least two stimulator output levels adjacent to each other with a 10/10 or with a 0/10 result (see Fig. 2). We tried to start suprathreshold and then diminished the output energy in steps of 1% until we reached the lower threshold. If the starting value was not suprathreshold we first increased the output levels in steps of 1% until we reached the upper threshold. Then we continued measuring with the output value 1% below the start value. With the Magstim stimulators output values were directly adjusted as a percentage of the maximal intensity. In contrast, the Dantec stimulator’s output power controller only provides a scale with 5% steps. We carefully adjusted the output intensity by estimating 1% steps on the scale, controlling the adjustments with the dI/dt values of the pulses measured and displayed directly by the machine. These values did not change continuously, but in discrete steps of 0.8 or 0.9 A/μs.

2.6. Data processing

For each threshold measurement a sigmoidal threshold function was fitted using the Boltzmann equation

$$y = \frac{A_1 - A_2}{1 + e^{(x - x_0)/\mathrm{d}x}} + A_2 \quad (1)$$

with A_1 and A_2 as the lower and upper boundaries, x_0 as the half-maximal value, and dx as the slope. A_1 and A_2 were fixed at 0 and 10, respectively. The motor threshold was defined as the half-maximal value x_0. This procedure is common in psychophysics (e.g. Gescheider, 1997).

In order to compare different thresholds, we also defined the following 3 threshold levels for each measurement: (i) the upper threshold (10/10) as the lower out of two output levels adjacent to each other with 10/10 CMAPs of >50 μV; (ii) the middle threshold (5/10) as the lowest output level evoking at least 5/10 CMAPs; and (iii) the lower threshold (0/10) as the higher of two output levels adjacent to each other with no CMAP of >50 μV. In Fig. 2 two representative measurements are shown demonstrating the Boltzmann fit as well as the 3 additional threshold definitions.

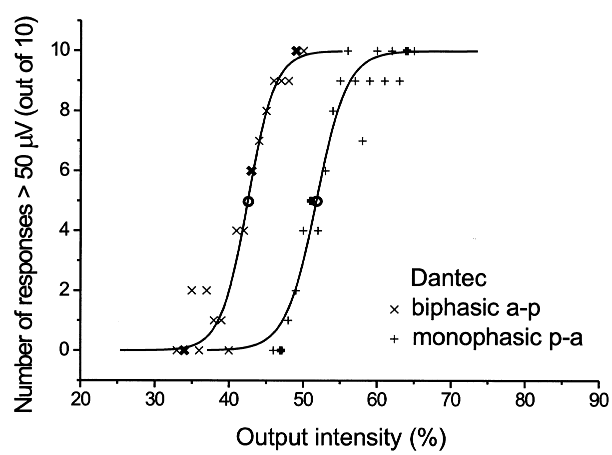

Fig. 2. Example of motor threshold calculation. Measurements of two different stimulator configurations of the Dantec stimulator are shown in one subject. On the abscissa the output intensity of the stimulator is given as a percentage. The ordinate depicts the number of CMAPs with an amplitude of >50 μV out of 10 trials. Boltzmann fits for both measurements are plotted. The circles indicate x_0, the half-maximal value of motor responses, defined as the motor threshold. For the configuration biphasic antero-posterior x_0 is 42.5%, while for monophasic postero-anterior x_0 is 51.8%. Three additional threshold values were determined by simple threshold rules (see Section 2). They are plotted in bold symbols. The 10/10 values are 49 and 64%, the 5/10 values are 43 and 51%, and the 0/10 values are 34 and 47% (biphasic antero-posterior and monophasic postero-anterior for each).

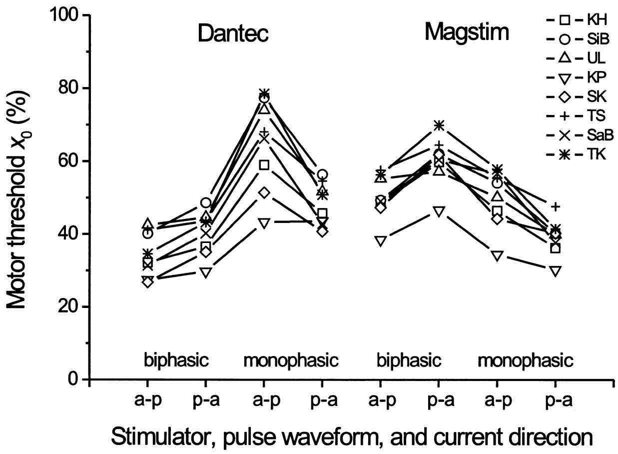

Fig. 3. Variation in motor thresholds of 8 subjects. On the abscissa the different stimulation configurations are given. Threshold values x_0 are given as a percentage of the maximal output of the stimulator used. Each symbol represents one subject.

3. Results

The variation in motor threshold intensities with changing stimulus parameters followed a consistent pattern. This is already visible in the raw data shown in Fig. 3, where threshold variations are shown as a function of stimulator type, pulse waveform and current direction for each subject investigated. The systematic variation is striking given the fact that the values measured in the different subjects varied by as much as 35.2% (Dantec monophasic antero-posterior, lowest threshold value 43.4%, highest threshold value 78.6%). As expected regarding the differences in the maximal energy stored by the stimulators (Table 1) the thresholds were consistently lower with the Magstim 200 (monophasic) than with the Magstim Rapid (biphasic). However, at the same maximal output energy provided by the Dantec stimulator, the biphasic pulse waveform was more effective than the monophasic pulse waveform (Fig. 3 and Table 2).

To compare the threshold intensities of the different stimulus configurations we normalized the threshold values of the individual subjects with respect to the intensity differences of the stimulators. We used the square root of the maximal energy stored (Table 1), which is approximately proportional to the electric field induced. In Fig. 4 the normalized mean values of motor thresholds are shown. These data were subjected to a 3-way analysis of variance (ANOVA) with factors of *stimulator type* (Dantec versus Magstim), *waveform* (biphasic versus monophasic), and *current direction* (antero-posterior versus postero-anterior). Significant main effects of *stimulator type* ($F(1,7) = 57.6$, $P < 0.0001$), *waveform* ($F(1,7) = 221.8$, $P < 0.0001$), and *current direction* ($F(1,7) = 10.7$, $P < 0.02$) were obtained. Thresholds were lower with the Dantec stimulator, with the biphasic waveform, and with the current direction oriented postero-anteriorly. However, the significant interaction of *waveform* × *current direction* ($F(1,7) = 45.7$, $P < 0.0003$) depicts a detailed pattern of the physiological effects of waveforms and current directions (Fig. 4). In the case of the biphasic waveform the postero-anterior current direction was more effective than the antero-posterior current direction with both stimulator types. The opposite pattern holds true for the monophasic waveform, which was less effective on the whole than the biphasic waveform.

The normalization to the square root of the maximal energy resulted in a systematic shift of threshold values obtained with the different stimulator types (Fig. 4). The mean ratio of the normalized thresholds Magstim/Dantec is 1.3 ± 0.08. This factor might reflect the differences in the geometry of the coils chosen for this study, resulting in a more effective stimulation of the brain with a given energy in case of the Dantec coil compared to the Magstim coil.

For practical reasons we calculated transformation factors from the raw data. They allow the direct transformation of relative intensity values of a given stimulator configuration (percentage of the maximal output of the given stimulator type) into the intensity values of another stimulator configuration. To this end we normalized each subject's motor thresholds (Fig. 3) with respect to the configuration with the lowest threshold. In all of the subjects this was the Dantec biphasic waveform in the antero-posterior direction. The transformation factors, i.e. the relative motor thresholds of the different stimulators with respect to Dantec biphasic antero-posterior, are given in Table 2.

Table 2
Relative motor thresholds, related to Dantec biphasic antero-posterior[a]

Stimulator	Pulse waveform	Current direction	Motor thresholds x_0	Relative threshold
Dantec	Biphasic	Postero-anterior	40.3 ± 6.1	1.17 ± 0.10
		Antero-posterior	34.5 ± 6.2	1
	Monophasic	Postero-anterior	48.4 ± 5.9	1.42 ± 0.12
		Antero-posterior	64.8 ± 12.7	1.88 ± 0.23
Magstim	Biphasic	Postero-anterior	60.3 ± 6.7	1.79 ± 0.31
		Antero-posterior	50.3 ± 6.2	1.48 ± 0.18
	Monophasic	Postero-anterior	39.3 ± 4.9	1.16 ± 0.17
		Antero-posterior	50.0 ± 8.0	1.46 ± 0.22

[a] Values are the mean ± SD. The relative motor thresholds allow the transformation of a stimulus intensity of a certain stimulator configuration (given as a percentage of the maximal output of the stimulator) into the equivalent stimulus intensity of a different stimulator configuration.

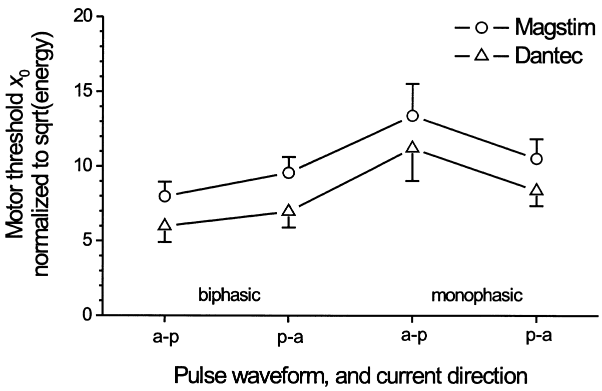

Fig. 4. Mean values of relative motor thresholds x_0 ($\pm$SD) of all 8 different stimulus configurations. The threshold values were normalized with respect to the square root of the maximal stored energy of the different stimulator types (Table 1). See text for results of ANOVA.

We compared the motor threshold values x_0 obtained with a Boltzmann fit with the values obtained by more common definitions using a simple rule as described above (Table 3). The 5/10 threshold values (the most commonly used threshold definition) were very close to x_0. The mean deviation calculated as the difference between x_0 and 5/10 in every individual measurement was $1.12 \pm 1.32\%$ (median 0.64%, maximum 5.88%) of stimulator output intensity. The ANOVA applied to the 5/10 threshold data revealed the same significant pattern as described for the x_0 threshold data. This also holds true for the 10/10 and 0/10 values. But, in contrast to the 5/10 values, the relative intensity values calculated as the ratio of a given threshold to the lowest value (Dantec biphasic antero-posterior in all cases) were slightly lower in the 10/10 definition than in x_0 (Table 3, relative values not shown). For example, the relative threshold for Dantec monophasic antero-posterior is 1.86 ± 0.23 (10/10) compared to 1.88 ± 0.23 (x_0). In contrast, the relative intensity values in 0/10 were slightly larger than x_0; for example, Dantec monophasic antero-posterior: 1.94 ± 0.22 (0/10) versus 1.88 ± 0.23 (x_0).

4. Discussion

The purpose of the present study was to compare the output energy of different stimulator types and pulse waveforms under physiological conditions. We chose the motor threshold of a relaxed small hand muscle of the dominant hemisphere. This is the best established method to determine interindividual differences in cortical excitability (e.g. Rossini et al., 1992, 1994; Triggs et al., 1994). It is a more precise measurement than the threshold for perception of a phosphene induced by stimulation of the occipital cortex (Afra et al., 1998; Aurora et al., 1998). Therefore, it is commonly used to adjust stimulation intensities in therapeutic applications of repetitive TMS on the prefrontal cortex (Pascual-Leone et al., 1996; Pridmore et al., 1998; Wassermann, 1998), assuming that excitability of different cortical areas does not differ within a subject. Despite the high interindividual variability in motor thresholds, we found significant differences between the mean thresholds with different stimulation configurations. Therefore, we can conclude that our stimulation technique suffices to attribute the obtained threshold differences to physical properties of the different stimulator configurations. The calculated ratios (Table 2) allow us to convert the intensity values (given as a percentage of the maximal output of the stimulator) in studies using a certain stimulus configuration into those measured with another stimulus configuration.

The normalization of the motor threshold values with respect to the maximum of the electric field applied by the different stimulator types (Fig. 4) revealed a distinct pattern of motor threshold variation with respect to pulse waveform and current direction in the brain. However, it also showed a striking systematic shift in motor thresholds when we compared the Dantec and the Magstim configurations. Both results, the differences in motor thresholds with different pulse forms and current directions as well as the differences between the values for the two stimulator brands, demonstrate that the stimulation energy itself is not sufficient to predict the physiological effect of TMS on the motor cortex. Aside from the stimulation energy the following

Table 3
Comparison of different threshold definitions[a]

Stimulator	Pulse waveform	Current direction	Threshold definition			
			Boltzmann fit x_0	10/10	5/10	0/10
Dantec	Biphasic	Postero-anterior	40.3 ± 6.1	44.6 ± 7.2	40.3 ± 6.1	35.5 ± 5.2
		Antero-posterior	34.5 ± 6.2	39.5 ± 6.9	34.4 ± 6.3	29.5 ± 4.5
	Monophasic	Postero-anterior	48.4 ± 5.9	55.3 ± 7.8	46.8 ± 5.9	43.3 ± 6.2
		Antero-posterior	64.8 ± 12.7	73.6 ± 16.1	64.5 ± 12.9	57.6 ± 12.0
Magstim	Biphasic	Postero-anterior	60.3 ± 6.7	66.0 ± 7.3	60.1 ± 6.7	56.0 ± 6.3
		Antero-posterior	50.3 ± 6.2	56.0 ± 7.5	49.6 ± 5.7	44.4 ± 5.6
	Monophasic	Postero-anterior	39.3 ± 4.9	44.8 ± 6.3	39.3 ± 5.1	35.1 ± 4.9
		Antero-posterior	50.0 ± 8.0	56.0 ± 10.6	49.8 ± 8.0	43.6 ± 7.4

[a] Mean values (±SD) of motor thresholds are given as a percentage of the output intensity of the stimulator.

aspects have to be taken into account as well: (i) the geometry of the figure-of-eight coils, which differs between Dantec and Magstim; and (ii) the difference between the physiological effects of monophasic and biphasic or polyphasic pulses. A straightforward model for calculating physiological effects from the given stimulator physics is still not available because the aspects mentioned are not fully understood yet. Furthermore, (iii) the exact site of cortical stimulation with respect to the field distribution is not known. Only answers to these 3 points will allow us to directly calculate the transformation factors we have established in Table 2 by means of the physiological approach.

4.1. Geometry of the figure-of-eight coils

The main difference in geometry is the angle between the two wings of the coil. They are arranged in a plane in the Magstim coil (180°), but are bent to an angle of 140° in the case of the Dantec coil. This bending compensates for the convexity of the skull. Unfortunately, the electric field distribution of the Dantec coil has not been calculated yet. Cohen et al. (1990) calculated the electric field distribution of a figure-of-eight coil with 180° and then showed that an angle of >180° leads to a more focal field. Inversely, an angle of <180° results in a less focal field distribution, but increases field strength. Our results show that this increase in field strength amounts to a factor of about 1.3. It is not clear yet whether only currents induced under the junction of the two wings contribute to the more effective depolarization, or if lateral parts of the two wings situated closely to the skull contribute to the physiological effect as well. Another difference between the two coils that contribute to the different field strengths observed is the mean diameter, which is larger in the Magstim coil (74 mm) than in the Dantec coil (60 mm). In general, smaller coils produce more intense fields close to their windings making them efficient in stimulating superficial structures. But field strength drops more rapidly with depth, resulting in less efficient stimulation of deeper structures (Epstein et al., 1990).

4.2. Physiological effects of monophasic and biphasic pulse waveforms

For the monophasic waveform it has been established that a current passing the motor cortex in a postero-anterior direction perpendicular to the central sulcus is more effective than one in the opposite direction (Brasil-Neto et al., 1992; Mills et al., 1992). Claus et al. (1990) reported that polyphasic pulses in general seem to be more powerful than monophasic ones. Furthermore, Brasil-Neto et al. (1992) mentioned that in contrast to the monophasic pulse a polyphasic one is more powerful if the first phase crosses the motor cortex in an antero-posterior direction. In a recent study, Maccabee et al. (1998) compared the effect of a polyphasic waveform with two damped waveforms, one of them comparable to the monophasic waveforms applied in the present study. They stimulated an in vitro preparation of an isolated nerve as well as the median nerve at the wrist of human subjects. Additionally, they simulated stimulation effects with a nerve model. The monophasic pulse was more effective if the current direction of the initial upstroke caused a depolarization at the membrane of the axons. In contrast, the threshold was higher if the initial upstroke of the monophasic pulse caused a hyperpolarization at the membrane. Also, the polyphasic waveform was more effective when the first phase of the pulse caused a hyperpolarization at the membrane than when the current direction caused a depolarization at the membrane. This was also found to be true when the median nerve was stimulated. Here, monophasic pulses were less effective.

Our data confirm the findings of Maccabee et al. (1998) for the scenario in the cerebral cortex. Much as they did in the in vitro nerve preparation we found that (i) a biphasic waveform is more powerful than a monophasic one when the first upstroke is identical (Dantec stimulator) or when the stimulation energy is normalized to the square root of the maximal energy stored (Magstim stimulators) and (ii) as far as the direction of the first upstroke is concerned, the most effective current direction in the brain for the biphasic pulse waveform was opposite to that for the monophasic waveform (Dantec and Magstim stimulators). In order to explain why the biphasic or polyphasic waveform is more effective if the first phase causes a hyperpolarization, Maccabee et al. (1998) argued that the initial hyperpolarization might increase the fraction of Na^+ channels available for the subsequent depolarizing phase. An alternative argument by the authors was that the duration of the depolarizing phase is relevant for the efficiency of stimulation. With the initial hyperpolarizing phase the subsequent depolarizing phase lasts a half-cycle of the whole stimulation sequence, compared to a quarter-cycle with the initial depolarizing phase. Both arguments might be relevant when stimulating the cerebral cortex. However, we must consider a third possible explanation for the different thresholds relating to different waveforms and current directions. It is conceivable that by reversing the current direction we depolarize different sets of cortical neurons with different thresholds.

Recently, Niehaus et al. (2000) investigated motor thresholds and amplitudes of CMAPs to different stimulus intensities using the Dantec Magpro stimulator. Much as in our study, they systematically varied pulse waveform and current direction. For the monophasic waveforms, they found the same pattern in motor threshold that we did. But, in contrast to our results, they did not find a significant difference in thresholds with the biphasic waveform when they compared the current directions postero-anterior versus antero-posterior. The most likely explanation for this striking difference might be the precision with which the coil position was maintained. With our stereotactic positioning device and the continuous visual feedback we were able to maintain a given coil position within a range of 1–2 mm. This precision cannot be reached by maintaining the coil position manually, as Niehaus et al. (2000) did.

4.3. Site of stimulation

To predict threshold differences in different field geometries we have to know the exact site of stimulation with respect to the field distribution. However, this also remains speculative. Maccabee et al. (1993) demonstrated that excitation of a peripheral nerve did not occur in the peak maximum of the induced electric field above the center of a figure-of-eight coil. Excitation started at the negative-going first spatial derivative peak of the electric field, which is normally shifted about 2–3 cm from the center of the coil. This only holds true for a straight, non-bent peripheral nerve in a homogeneous environment. Bending the nerve shifted the excitation site towards the bend, as is the case with cut ends of the nerve. Therefore, it has been argued that in the cortex, where axons might be bent or end within a small sample volume, the maximum of the electric field under the center of the coil depolarizes best and with a lower threshold than would be the case with a non-bent nerve (Amassian et al., 1992; Nagarajan et al., 1997). In the present study, we chose a site of stimulation where the muscle response was maximal ('hot spot'). This is the technique commonly used in threshold measurements (e.g. Mills and Nithi, 1997; Triggs et al., 1994; Ziemann et al., 1998a). With the stereotactic positioning device we were able to maintain this site precisely throughout the whole experiment so that the different stimulator configurations were tested at the same site.

4.4. Threshold definition

To determine the motor threshold we applied the so-called 'method of constant stimuli' which is commonly used for threshold measurements in psychophysics (e.g. Gescheider, 1997). The threshold values x_0 obtained after fitting a threshold function to the measured data did not substantially differ from the threshold values obtained using the 5/10 definition (middle threshold, 5 out of 10 stimuli exceed the defined threshold amplitude). Since the 5/10 method (e.g. Ziemann et al., 1998a) is much less time-consuming than the method of constant stimuli, our results allow the conclusion that the former method is sufficient and there is no need to perform the latter in order to obtain reliable motor threshold values.

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