Conclusions
Supramaximal CMAPs can be obtained in most normal subjects. In subjects exhibiting confirmed supramaximal CMAPs in response to MRS, not only the latency of these CMAPs but also their amplitude and area can be clinically useful, excluding CMAPs in the APB muscle.

Keywords compound muscle action potential; magnetic stimulation; motor-evoked potential; peripheral nerve

Magnetic stimulation has been widely used to evaluate central and peripheral motor conduction in humans ever since its initial clinical application.[1] Response latency has frequently been used as a parameter aiding in the diagnosis of many relevant conditions. Response amplitude, in contrast, has rarely been used for diagnostic purposes, probably because magnetic stimulation cannot always evoke supramaximal responses.[2-4]

In this study, we demonstrate that supramaximal responses can be obtained in response to magnetic cervical motor root stimulation (MRS) by using a magnetic stimulator that is more powerful than most. We compared supramaximal responses obtained in response to MRS with those obtained in response to electrical stimulation at the wrist, Erb's point (EP), and the cervical motor roots (Root). Furthermore, we studied the relationship between response latency and body height.

Subjects and methods

Subjects

The subjects enrolled in this study were 36 right-handed healthy volunteers (23 men and 13 women; age range, 24-57 years [mean ± SD, 34.2 ± 7.4 years]) without any history of cervical spondylosis, diabetes mellitus, central nervous system disorders, peripheral neuropathies, or other neuromuscular diseases. The mean ± SD of their body heights was 167.3 ± 8.0 cm (range: 153-182 cm). One patient was recruited to show the clinical use of our method, which is described in detail in the *Results* section. The results of this patient will be given as a case presentation. Written informed consent was obtained from all subjects. The experiments were performed according to the Declaration of Helsinki; and the procedures were approved by the Ethics Committee of the University of Tokyo.

Recording

During the examination, subjects were seated on a reclining chair with their arms relaxed on the arm rests. Compound muscle action potentials (CMAPs) were recorded from the following three distal muscles: the first dorsal interosseous ([FDI] C8-T1; ulnar nerve), the abductor digiti minimi ([ADM] C8-T1; ulnar nerve), and the abductor pollicis brevis ([APB] C7-T1; median nerve). Disposable silver-silver chloride disk electrodes, 9 mm in diameter, were placed in a belly-tendon montage. Signals were amplified through a Biotop amplifier (GE Marquette Medical Systems, Tokyo, Japan) with filters set at 20 Hz and 3 kHz, and recorded onto a computer (Signal Processor DP-1200; GE Marquette Medical Systems). Subjects' skin temperature was maintained at around 33°C-34°C. At least three CMAPs, either supramaximal or at the stimulus intensity of maximal stimulator output, were recorded from each subject to confirm the reproducibility of the findings. The peak-to-peak amplitude (mV), negative area (mV × milliseconds), and onset latency (milliseconds) of each CMAP were measured. The SPSS 14 statistical software package (SPSS, Chicago, IL) was used for all statistical analyses. *P* values less than .05 were considered significant.

Stimulation

MRS was delivered through a custom-built enhanced power Magstim 200 stimulator (Magstim, Whitland, UK) with a round coil 10 cm in mean diameter; this stimulator is about 1.4 times as powerful as the commercially available Magstim 200 stimulator. Electrical stimulation at the wrist was delivered through a conventional electrical stimulator (Electronic stimulator 3F46, NEC-San Ei, Tokyo, Japan), whereas electrical stimulation at the EP and the Root (electrical cervical motor root stimulation [ERS]) was delivered through a D180A high-voltage electrical stimulator (Digitimer, Welwyn Garden City, UK).

For MRS, the upper edge of a round coil was positioned on the seventh cervical (C7) spinous process so that a part of its edge was over the exit of each spinal nerve from the intervertebral foramina. With the coil firmly held against the spine, an examiner pulled the subject's chest backward so that the coil was as close as possible to the target spinal nerves. The coil currents were directed clockwise as seen from behind in our examination of the right hand muscles so that the induced currents in the body were directed from the muscles to the spinal cord at the upper edge of the coil (Figure 1). A previous study has confirmed that this direction is suitable for producing maximal CMAPs (minimal threshold) in MRS.[4] The stimulus intensity was gradually increased until supramaximal CMAPs were obtained.

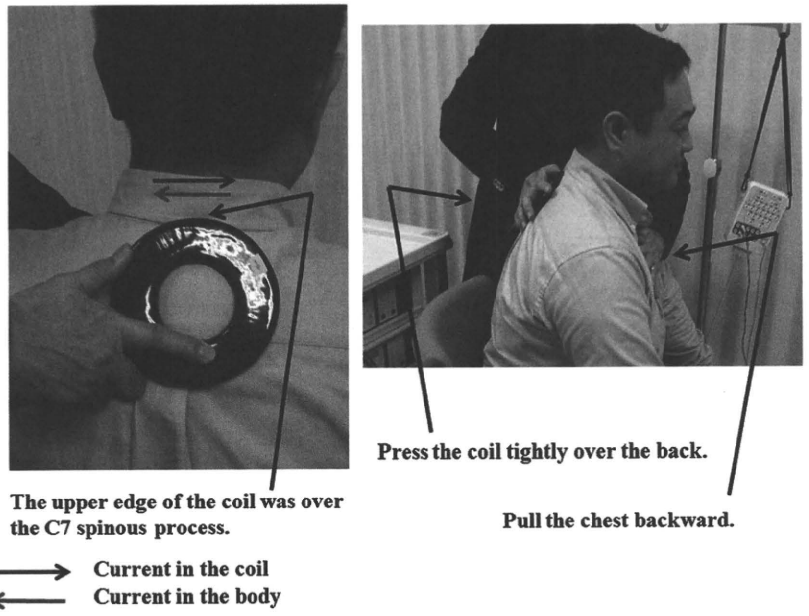

Figure 1 Back and lateral views of magnetic cervical motor root stimulation. The examiner is firmly pressing a round coil to the subject's back and forcefully pulling his chest backward.

We considered a supramaximal CMAP to have been obtained only when the size of superimposed CMAPs was saturated before the stimulus intensity reached a value equal to 1.3 times the lowest intensity that resulted in a maximal CMAP.

Electrical stimuli were applied at the wrist, EP, and Root. At the wrist and EP, each anode was placed a few centimeters proximal to the cathode. At the Root, a cathode was placed over the C7 spinous process, and an anode was placed 5 cm rostral to it.[5,6] All electrodes were then securely attached to the skin. The stimulus intensity was increased gradually until a supramaximal CMAP was obtained (i.e., until the stimulus intensity reached a value 1.3 times that of the lowest intensity capable of eliciting a maximal CMAP).

Experiment 1: Collision experiment

Nine subjects participated in this experiment. Given that MRS activates several nerves simultaneously because each root connects with several peripheral nerves, it seemed likely that volume conduction from nontarget muscles might affect the size of CMAPs occurring in response to MRS. Our collision experiment was designed to determine the degree to which this occurs.[7]

CMAPs from the right hand muscles were elicited by simultaneous MRS and electrical stimulation at the wrist and recorded. We expected that, if CMAPs were produced in response to MRS from the target muscle only, MRS would elicit no potentials because the orthodromic descending impulses generated by MRS would completely collide with the antidromic ascending impulses generated by wrist stimulation. If, on the other hand, some other nontarget muscles were contributing to the CMAPs in response to MRS (volume conduction effect), or if the recorded muscle were partly innervated by nontarget nerves, then MRS would provoke some potential at a longer latency than CMAPs not contaminated by volume conduction. The amplitude of the later potential was expressed as a percentage relative to that of the CMAPs in response to wrist stimulation. This value indicated the amount of volume conduction from other muscles that was contaminating the CMAPs. In our experiments, wrist stimulation was delivered to the ulnar (for FDI and ADM) or median nerve (for APB).

Experiment 2: Analyses of supramaximal CMAPs evoked by MRS

All 36 subjects participated in this experiment. CMAPs were recorded from the right FDI and ADM muscles in all subjects (72 muscles). APB was excluded because of considerable volume conduction (discussed in *Results, experiment 1*).

We determined how often supramaximal CMAPs could be obtained in response to MRS. If supramaximal CMAPs were obtained, the ratios of the amplitude and area of MRS-induced CMAPs and of CMAPs induced by electrical stimulation to the EP to those of wrist stimulation-induced CMAP were calculated, as were the ratios of the amplitude and area of MRS-induced CMAP to those of CMAPs induced by electrical stimulation to the EP.

To analyze the relationship between body height and CMAP latency, we performed a linear regression analysis.

Moreover, to analyze the difference between the responses generated in the two sides of each individual's body, CMAPs were also recorded from the left FDI and ADM muscles in 22 of 36 subjects (44 muscles).

Experiment 3: Comparison between MRS and ERS

Twenty-two subjects exhibiting supramaximal CMAPs participated in this experiment. CMAPs were recorded from bilateral FDI and ADM muscles. To confirm supramaximal CMAPs, we compared the amplitudes of MRS-induced CMAPs with those of ERS-induced CMAPs using the paired *t* test.

Results

Subjects reported that the discomfort caused by MRS delivered by our high-power stimulator was not different from that caused by MRS delivered by a standard stimulator; the form of MRS used in the present study was well tolerated by all subjects. No side effects were noted. Figure 2 illustrates an example of supramaximal CMAPs recorded from the FDI of one subject.

Experiment 1: Collision experiment

Representative waveforms of the collision experiment are shown in Figure 3. The amplitudes of late responses were very small in the FDI (Figure 3, left) and the ADM (data not shown), whereas responses of considerable amplitude were elicited in the APB (Figure 3, right). The amplitudes of the later responses, expressed as percentages relative to the CMAP amplitudes, were 8.2% ± 3.0% in the FDI, 3.2% ± 1.6% in the ADM, and 28.8% ± 15.0% in the APB (mean ± SD).

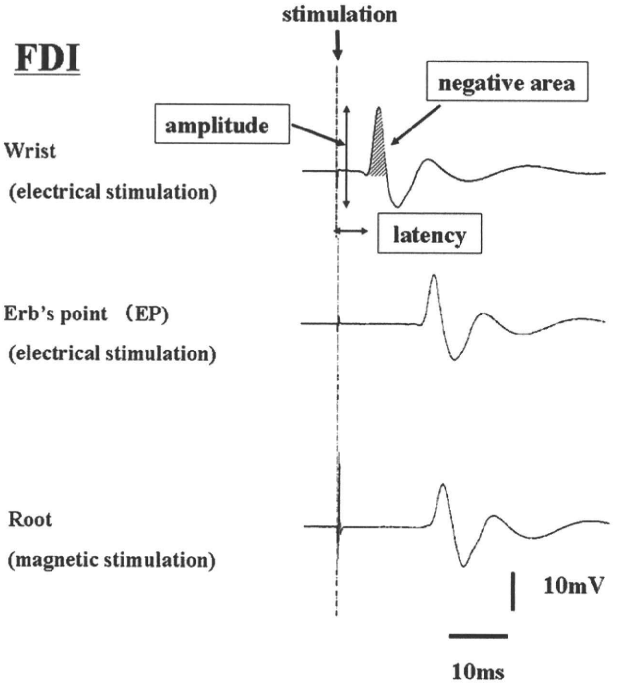

Figure 2 Representative waveforms of compound muscle action potentials (CMAPs) in one subject. CMAPs are elicited by means of electrical stimulation at the wrist and at Erb's point (EP) as well as by means of magnetic stimulation at the cervical motor roots (Root), and recorded at the first dorsal interosseous (FDI) muscle.

Experiment 2: Analyses of supramaximal CMAPs evoked in response to MRS

In 32 of 36 subjects (19 men, 13 women; age range 23-57 years [mean ± SD, 34.7 ± 7.6 years]; body height 153-179 cm [mean ± SD, 165.9 ± 7.3 cm]), MRS induced supramaximal CMAPs, that is, CMAPs did not increase in size even when the stimulus intensity was increased to

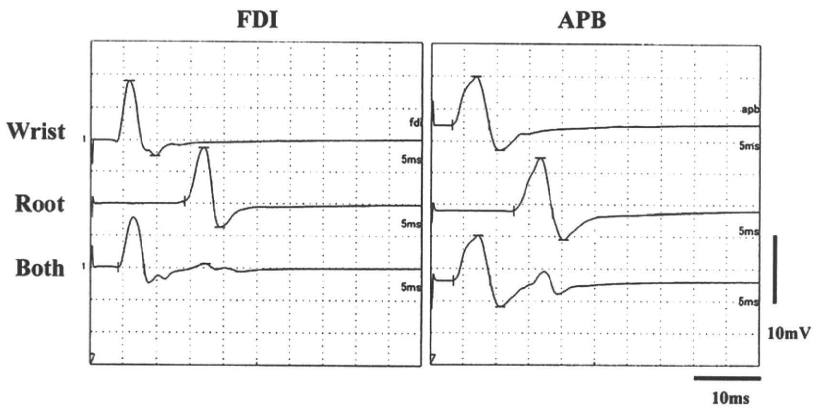

Figure 3 Responses in collision experiment. Compound muscle action potentials (CMAPs) elicited by means of electrical stimulation at the wrist, magnetic stimulation at the cervical motor roots (Root), and simultaneous stimulation at the wrist and Root are shown at the first dorsal interosseus (FDI) (left) and the abductor pollicis brevis (APB) (right). At the wrist, the ulnar nerve is stimulated to elicit responses from the FDI and the median nerve is stimulated to elicit responses from the APB. A very small late response is obtained by simultaneous stimulation in the FDI, whereas a later response of considerable size occurs in the APB.

1.3 times the minimal value that induced a maximal CMAP. This final intensity corresponded to 60-95% of the maximal stimulator output. In the four remaining subjects, supramaximal CMAPs could not be elicited even by using the maximal stimulator output; all four subjects were comparatively large and deep-chested men with heights ranging from 176-182 cm.

The amplitude, area and latency data obtained from the 32 subjects exhibiting supramaximal CMAPs are shown in Table 1. In the FDI, the CMAP amplitude ratio of Root/EP was 91.9% ± 6.7% (mean ± SD); the lowest normal limit was 78% (mean −2 SD). The area ratio of Root/EP was 96.8% ± 9.1%; the lowest normal limit was 78%. In the ADM, the CMAP amplitude ratio of Root/EP was 93.5% ± 8.6%; the lowest limit was 72%. The area ratio of Root/EP was 94.7% ± 8.0%; the lowest limit was 78%.

In the FDI, the correlation between CMAP latency after MRS and body height is shown in Figure 4. A significant and positive linear relation was observed ($P < .001$; latency = 0.11 × body height − 5.04). A similar correlation was observed in the ADM ($P < .001$; latency = 0.12 × body height − 6.74).

Experiment 3: Comparison between MRS and ERS

Among the 22 subjects who participated in this experiment, there was no significant difference in amplitude, area or latency between CMAPs occurring in response to MRS and those occurring in response to ERS in either the FDI or the ADM muscles (FDI amplitude: MRS 13.5 ± 3.1 mV, ERS 13.2 ± 3.4 mV, $P = .218$; area: MRS 19.7 ± 4.5 mV × millisecond, ERS 19.2 ± 4.8 mV × millisecond, $P = .077$; latency: MRS 12.9 ± 1.0 millisecond, ERS 12.9 ± 1.0 millisecond, $P = .609$; ADM amplitude: MRS 11.7 ± 2.2 mV, ERS 11.8 ± 2.5 mV, $P = .830$; area: MRS 19.8 ± 4.1 mV × millisecond, ERS 19.5 ± 4.4 mV × millisecond, $P = .183$; latency: MRS 12.6 ± 1.2 milliseconds, ERS 12.6 ± 1.2 milliseconds, $P = .333$).

Case presentation

Here we report on one patient whose response to MRS provided us with clinically useful information concerning the proximal regions of his peripheral nerves.

A 57-year-old man complained of acute shoulder pain and had muscular weakness of the right arm develop 3 days later. The clinical diagnosis was neuralgic amyotrophy. Conventional nerve conduction studies were all normal. F-wave latency was within the normal range, although the occurrence rate of F-waves was reduced to 50% of normal. Figure 5 shows CMAPs from the right ADM elicited in response to MRS or electrical stimulation at several sites. The CMAPs in response to electrical stimulation at the

Table 1 Data from subjects exhibiting supramaximal CMAPs

	FDI	ADM
Peak-to-peak amplitude (mV)		
Wrist	15.9 ± 4.0	15.6 ± 3.3
EP	14.6 ± 3.5	12.8 ± 2.7
Root	13.4 ± 3.2	11.9 ± 2.5
Root (laterality)	2.1 ± 1.7	2.0 ± 1.7
Ratio (%)		
EP/wrist	92.6 ± 10.6 (77-125)	82.7 ± 7.4 (64-98)
Root/wrist	85.2 ± 12.5 (60-118)	77.3 ± 10.0 (53-98)
Root/EP	91.9 ± 6.7 (78-112)	93.5 ± 8.6 (75-123)
Negative area (mV × milliseconds)		
Wrist	20.4 ± 5.2	23.5 ± 5.4
EP	20.4 ± 5.3	20.6 ± 4.4
Root	19.6 ± 4.7	19.4 ± 4.2
Root (laterality)	3.1 ± 2.2	4.3 ± 3.5
Ratio (%)		
EP/wrist	100.0 ± 7.9 (84-117)	88.4 ± 8.2 (71-113)
Root/wrist	96.9 ± 11.8 (74-125)	83.8 ± 10.5 (57-109)
Root/EP	96.8 ± 9.1 (76-123)	94.7 ± 8.0 (78-112)
Onset latency (milliseconds)		
Wrist	3.7 ± 0.4	2.8 ± 0.4
EP	11.8 ± 1.0	11.8 ± 1.1
Root	12.8 ± 1.0	12.6 ± 1.2
Root (laterality)	0.5 ± 0.4	0.3 ± 0.3
EP-Root	1.0 ± 0.4	0.7 ± 0.3

Data are shown as mean ± SD (range). ADM = abductor digiti minimi; CMAPs = compound muscle action potentials; EP = Erb's point; FDI = first dorsal interosseus; Root = cervical motor roots; SD = standard deviation.

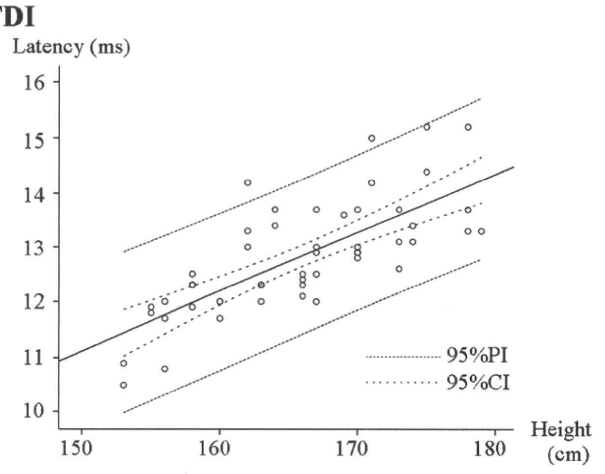

Figure 4 Significantly positive correlation between compound muscle action potential (CMAP) latency and body height. Data from the first dorsal interosseus (FDI) muscle are plotted. The formula for the relationship between latency and body height is as follows: latency = 0.11 × body height – 5.04 ($P < .001$, $R^2 = 0.55$). PI = prediction interval; CI = confidence interval.

wrist, below the elbow, and at the EP were all normal in amplitude, area, and latency. The supramaximal CMAP that occurred in response to MRS, however, had an amplitude that was obviously smaller than those of the other distal CMAPs. The amplitude of the CMAP in response to MRS was 40% of that of the CMAP in response to EP stimulation, which itself was smaller than the mean –2 SD (72%) of our normal values shown previously. Based on these results, we concluded that a conduction block was present between these two sites, that is, between the brachial plexus and the exit of the cervical spinal nerves from the intervertebral foramina. The patient's symptoms improved after treatment with intravenous immunoglobulin. After the symptoms had improved, the amplitude of his CMAPs occurring in response to MRS recovered to 96% of that of his CMAPS occurring in response to EP stimulation.

Discussion

The current data show that magnetic stimulation can be useful for evaluating conduction in the proximal regions of peripheral nerves as well as for central motor conduction studies. If this is confirmed, magnetic stimulation may come to be used in the diagnosis of neuropathies such as inflammatory demyelinating polyneuropathy,[8,9] brachial plexus injury,[10] and radiculopathy.[1,3,9] Magnetic or electrical stimulation over the cervical enlargements is often termed motor "root" stimulation, but neither method actually activates the spinal motor roots; instead, stimulation is delivered to the spinal nerves as they exit from the spinal canal through the intervertebral foramina.[2,4,11,12] Accordingly, "spinal nerve stimulation" would be a more correct nomenclature; however, because MRS has been commonly used, we use this term to describe our method in this article.

Several reports have demonstrated the clinical usefulness of data acquired through MRS, especially data on the latency of responses.[2,3,13,14] Data on the amplitude and area of responses, in contrast, have rarely been used as parameters for evaluation, probably because MRS cannot always elicit supramaximal CMAPs. The reported amplitudes of CMAPs occurring in response to MRS[2,3] have ranged from 10%-45% to 9%-100% and 16%-77% of the amplitudes of CMAPs occurring in response to peripheral nerve stimulation[4] in normal subjects. In our study, the amplitudes of CMAPs occurring in response to MRS ranged from 78%-100%. Moreover, supramaximal CMAPs could be obtained in 32 of 36 subjects, and the occurrence of supramaximal CMAPs in these subjects was verified by using high-voltage electrical stimulation. Our success in obtaining supramaximal CMAPs from most of the subjects might be explained by our use of a high-power magnetic stimulator that is about 1.4 times as powerful as commercially available stimulators. Another important technical point is that we pressed the coil firmly to the back of each subject while forcefully pulling the chest backward to place the coil as close as possible to the target spinal nerves.

Supramaximal stimulation is necessary for measurement of the CMAP amplitude in the detection of conduction blocks in neurophysiologic studies.[15,16] In the current study, the difference in amplitude between CMAPs in the ADM induced by EP stimulation and those induced by Root stimulation was about 6.5%; the highest normal limit (mean –2 SD) was 28%. This result is similar to one previously reported by Arunachalam et al.,[15] who conducted

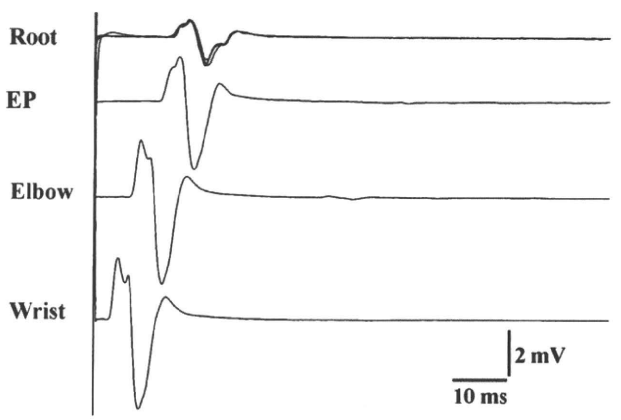

Figure 5 Compound muscle action potentials (CMAPs) in a patient with neuralgic amyotrophy. CMAPs from the right abductor digiti minimi (ADM) were elicited by means of electrical stimulation at the wrist, below the elbow, and at Erb's point (EP). CMAPs were also elicited by means of magnetic stimulation at the cervical motor roots (Root). The amplitude of MRS-induced CMAPs was only 40% of that of EP stimulation-induced CMAPs.

cervical motor root stimulation using a high-voltage electrical stimulator. Therefore, when supramaximal MRS is achieved and the difference in amplitude between CMAPs induced by EP stimulation and those induced by Root stimulation is above the highest normal limit, this indicates a conduction block, as in the case presentation.

The collision experiment revealed that volume conduction accounted for less than 9% of the responses in the FDI and less than 4% of those in the ADM. In the APB, however, volume conduction was substantially greater (by approximately 30%) than in the other two muscle. These amounts of volume conduction are similar to those previously reported in a study that used a high-voltage electrical stimulator.[15] The high-volume conduction commonly observed in CMAPs from the APB in response to both MRS and ERS is explained by the fact that the APB is surrounded by ulnar-nerve-innervated muscles (the flexor pollicis brevis and the adductor pollicis), as well as by the fact that APB itself is sometimes partly innervated by the ulnar nerve. Based on our results, we concluded that MRS-induced CMAPs from the APB are not suitable for amplitude evaluation.

A positive correlation between the latency of CMAPs occurring in response to MRS and body height has been reported.[3,13,17] Cervical motor root stimulation by means of a needle electrode has revealed an identical correlation.[18] Our normal values were consistent with these previously described values, and the formulas obtained through our study are useful for the evaluation of the latency of CMAPs in response to MRS.

ERS is an alternative method for cervical motor root stimulation, but magnetic stimulation offers two advantages over it. First, magnetic stimulation produces less discomfort than electrical stimulation, which can sometimes elicit severe pain. Second, magnetic stimulation can be used for patients on whose skin it is not possible to fix cutaneous electrodes because of skin problems.[19]

Our study has some limitations. First, the number of subjects was fairly small and their age range was fairly restricted; this makes it less likely that our data are normative. Data from additional healthy subjects must be acquired to make our data set comprehensive and normative. Second, supramaximal CMAPs cannot be obtained in all subjects. If CMAPs continue to enlarge as stimulation intensity increases, we cannot exclude the possibility of suboptimal stimulation. If this is the case, then amplitude inconsistencies in CMAPs occurring in response to MRS do not necessarily indicate conduction blocks in patient analyses. Another disadvantage of our stimulation method is the current spread to distal regions far from the expected stimulation point at very high stimulus intensities (such as stimulation with 95% or 100% maximal stimulator output). In this case, the existence of a conduction block may be missed because the stimulation site may jump to a more distal position lying beyond the region of the conduction block. Despite these limitations, however, MRS can provide us with useful information about proximal motor conduction when supramaximal CMAPs are obtained in response to MRS, as in the case study reported here.

This study has yielded two new findings with regard to MRS: (1) though previous studies have reported otherwise, supramaximal CMAPs can be elicited in response to MRS in most normal subjects. The amplitude and area of CMAPs can also be used as diagnostic parameters in patients who exhibit supramaximal CMAPs. (2) CMAP latency correlates significantly with body height; the formulas for this relationship have been provided.

Acknowledgments

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Prominent cauda equina involvement in patients with chronic inflammatory demyelinating polyradiculoneuropathy

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ABSTRACT

In chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), it has not been well known which segment of the peripheral nerves, distal or proximal, is more often involved in electrophysiological examination. This study compares nerve conductions at proximal segments with those at distal segments in 11 patients with CIDP. To obtain cauda euqina conduciton time (CECT), compound muscle action potentials (CMAPs) were elicited by magnetic stimulation using a MATS coil from the abductor hallucis muscle. CECT was prolonged in 9 patients (81.8%), whereas the ankle–knee conduction was delayed in 4 (36.4%). The proximal segments are more frequently involved than the distal segments in this disorder.

1. Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a relapsing or chronically progressive disorder most commonly presenting with limb weakness, distal sensory disturbance, and hyporeflexia [1,2]. In the process of demyelination, the immune-mediated pathogenesis such as unknown antibodies or some other circulating factors might be involved [2,3]. Nerve conduction studies in the distal extremities usually show slowing of motor conduction [2,3]. F-wave studies also reveal the high frequency of proximal peripheral nerve lesions [4,5]. However, F-wave method alone cannot allow us to localize the peripheral nerve lesions. Therefore, it has not been well known which segment of peripheral nerves, distal or proximal, is more often involved in electrophysiological examination.

Recently, we have developed a novel magnetic stimulation method to measure cauda equina conduction time (CECT) using a specially devised powerful coil designated as a Magnetic Augmented Translumbosacral Stimulation (MATS) coil [6,7]. This method enables us to activate the spinal nerves at the both proximal and distal sites of cauda equina.

In this investigation, we compared nerve conductions at proximal segments with those at distal segments using the above mentioned new stimulation method as well as the conventional nerve conduction studies.

2. Subjects and methods

2.1. Subjects

We studied 11 CIDP patients (6 men and 5 women) diagnosed according to the established diagnostic criteria [8]. The age and body height of the patients were 54.1 ± 16.8 (mean ± standard deviation (SD); range 26–83 years and 163.5 ± 10.1 (145–175) cm, respectively. Patients in whom reliable compound muscle action potentials (CMAPs) were unobtainable by electrical stimulation or magnetic stimulation were excluded from this study. The clinical profile of the patients is summarized in Table 1. Their disabilities were assessed using the Hughes functional grading scale (grade 4 = bound to bed, grade 3 = able to walk 5 m with aid, grade 2 = ambulates independently, and grade 1 =minimal signs and symptoms and able to run) [9].

Informed consent to participate in this study was obtained from all subjects. The protocol was approved by the Ethics Committee of the University of Tokyo. The experiments were conducted in accordance with the ethical standards of the Declaration of Helsinki.

2.2. Stimulation, recording and analysis

During the examination, patients lay comfortably on a bed in prone position. CMAPs were recorded from the abductor hallucis

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Table 1
Clinical profile and results of 11 CIDP patients.

Case	Age	Sex	Disease duration	Hughes scale	Diagnostic categories	MCV (m/s)	CECT (ms)
1	42	M	6 months	3	Definite CIDP	42	5.1
2	51	M	7 months	1	Possible CIDP	44	3.8
3	33	F	1 year	2	Definite CIDP	50	6.9↑
4	57	F	1 year	2	Definite CIDP	45	10.1↑
5	71	M	1 year	2	Definite CIDP	31↓	9.1↑
6	26	F	5 years	1	Definite CIDP	31↓	10.3↑
7	57	M	7 years	2	Definite CIDP	42	5.9↑
8	66	F	11 years	2	Definite CIDP	38↓	7.1↑
9	44	M	19 years	3	Definite CIDP	27↓	9.8↑
10	63	F	24 years	4	Definite CIDP	41	8.1↑
11	83	M	29 years	4	Definite CIDP	44	6.8↑
Normal values (mean ± SD, $n = 20$ subjects)						49.3 ± 4.4	3.7 ± 0.8
Mean − or + 2.5SD (lower limit or upper limit)						38.3	5.7

MCV: motor conduction velocity, CECT: cauda equina conduction time, SD: standard deviation, ↓: abnormal decrement, ↑: abnormal increment.

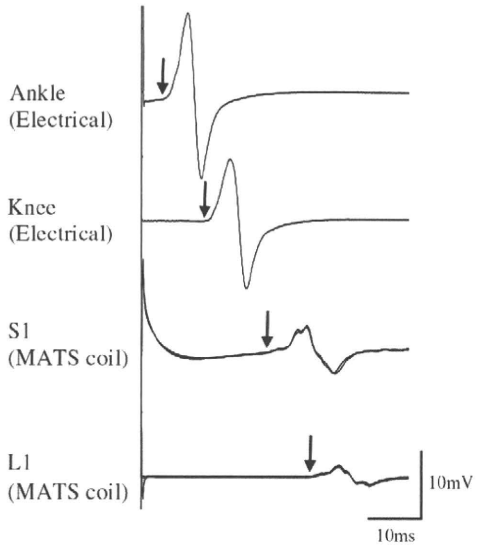

Fig. 1. MATS coil stimulation study in case 3. Motor conduction velocity (MCV) between ankle and knee is normal (50.0 m/s). In contrast, CECT calculated by using S1 and L1 level MATS coil stimulations is prolonged (6.9 ms, upper limit of normal values is 5.7 ms).

muscle (AH) on the more affected side. Disposable silver–silver chloride disc electrodes of 9 mm diameter were placed in a belly-tendon montage over AH. Signals were amplified with filters set at 20 Hz and 3 kHz and recorded by a computer (Neuropack MEB-9100, Nihon Kohden, Japan). The skin temperature was maintained at around 32–33 °C.

For distal segment nerve conduction studies, the posterior tibial nerve was stimulated at the posterior medial malleolus of ankle and the popliteal fossa with a conventional electrical stimulator (Neuropack MEB-9100, Nihon Kohden, Japan). The motor conduction velocity (MCV) was calculated dividing the ankle–knee length by the latency difference. For proximal segment conduction studies (measuring CECT), magnetic stimulation was performed with a monophasic stimulator, Magstim 200 (The Magstim Co, UK) using a MATS coil (diameter 20 cm, 0.98 T; The Magstim Co, UK) [6,7]. For the most distal cauda equina level stimulation, the edge of MATS coil was positioned over the 1st sacral (S1) spinous process for inducing currents to flow 60° downward from horizontal direction [6]. The most proximal cauda equina was activated by the MATS coil whose edge was positioned over the 1st lumbar (L1) spinous process for inducing currents to flow upward [7]. The CECT was obtained by subtracting the CMAP latency to S1 level stimulation from that to L1 level stimulation.

CECT and MCV of the patients were compared to those of age and body height matched control subjects. The frequencies in abnormities of CECT and MCV were statistically compared between two groups using Wilcoxon's signed rank test. P values less than 0.05 were considered to be significant.

3. Results

Fig. 1 displays the representative CMAPs in a patient with CIDP (case 3). Although MCV calculated by using ankle and knee stimulations was normal (50.0 m/s), CECT calculated by using S1 and L1 level MATS coil stimulations was abnormally prolonged (6.9 ms, upper limit of normal values is 5.7 ms). The results of MCV and CECT in all the patients are summarized in Table 1. MCV was abnormally decreased in 4 patients (36.4%). CECT was significantly prolonged in 9 patients (81.8%). All the patients with prolonged CECT had been suffering from CIDP for more than one year. The other 2 patients with normal CECT (cases 1 and 2) had relatively short disease duration (6 and 7 months). CECT prolongation was observed at a significantly higher frequency compared to MCV decrease ($P = 0.0253$).

4. Discussion

CECT prolongation was more frequently observed as compared to MCV reduction in CIDP. It suggests the high frequent spinal nerve involvement in the spinal canal. Prior studies of magnetic resonance images reveal that the spinal nerves in the spinal canal are frequently involved in CIDP [10–12]. Therefore, our results have verified the prominent spinal nerve involvement in the spinal canal electrophysiologically.

Similar comparison in the upper extremities has been reported by Inaba et al. [13]. The cervical root conduction time in the spinal canal was prolonged in 7 out of 11 CIDP patients (63.6%) and MCV between wrist and elbow was decreased in 9 patients (81.8%). These values should not be directly compared with our results because the spinal canal segment of cervical spinal nerves is very short as compared with cauda equina. Considering the short length, this indicates that the cervical spinal nerves in the spinal canal also must be very frequently involved.

Why are the segments within a spinal canal so frequently involved? This might be explained by some anatomical reasons. The blood nerve barrier needs to be broken for the demyelinating process of distal peripheral nerves [14]. In contrast, the proximal spinal nerves in the spinal canal are lacking blood nerve barriers and these are directly exposed to cerebrospinal fluid [15]. These anatomical structures might allow unknown antibodies or some other circulating factors to gain direct access to the spinal nerves including the cauda equina. Based on these discussions, we conclude that the cauda equina is very vulnerable to the immunological attack in CIDP.

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Guidelines

Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research ☆

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ABSTRACT

This article is based on a consensus conference, which took place in Certosa di Pontignano, Siena (Italy) on March 7–9, 2008, intended to update the previous safety guidelines for the application of transcranial magnetic stimulation (TMS) in research and clinical settings.

Over the past decade the scientific and medical community has had the opportunity to evaluate the safety record of research studies and clinical applications of TMS and repetitive TMS (rTMS). In these years the number of applications of conventional TMS has grown impressively, new paradigms of stimulation have been developed (e.g., patterned repetitive TMS) and technical advances have led to new device designs and to the real-time integration of TMS with electroencephalography (EEG), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Thousands of healthy subjects and patients with various neurological and psychiatric diseases have undergone TMS allowing a better assessment of relative risks. The occurrence of seizures (i.e., the most serious TMS-related acute adverse effect) has been extremely rare, with most of the few new cases receiving rTMS exceeding previous guidelines, often in patients under treatment with drugs which potentially lower the seizure threshold.

The present updated guidelines review issues of risk and safety of conventional TMS protocols, address the undesired effects and risks of emerging TMS interventions, the applications of TMS in patients with

☆ A Consensus Statement from the International Workshop on "Present and Future of TMS: Safety and Ethical Guidelines", Siena, March 7–9, 2008.

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implanted electrodes in the central nervous system, and safety aspects of TMS in neuroimaging environments. We cover recommended limits of stimulation parameters and other important precautions, monitoring of subjects, expertise of the rTMS team, and ethical issues. While all the recommendations here are expert based, they utilize published data to the extent possible.

Contents

1. Introduction

Transcranial magnetic stimulation (TMS) is a neurostimulation and neuromodulation technique, based on the principle of electromagnetic induction of an electric field in the brain. This field can be of sufficient magnitude and density to depolarize neurons, and when TMS pulses are applied repetitively they can modulate cortical excitability, decreasing or increasing it, depending on the parameters of stimulation, even beyond the duration of the train of stimulation. This has behavioral consequences and therapeutic potential.

The last decade has seen a rapid increase in the applications of TMS to study cognition, brain-behavior relations and the pathophysiology of various neurologic and psychiatric disorders (Wassermannn and Lisanby, 2001; Kobayashi and Pascual-Leone, 2003; Gershon et al., 2003; Tassinari et al., 2003; Rossi and Rossini, 2004; Leafaucheur, 2004; Hoffman et al., 2005; Couturier, 2005; Fregni et al., 2005a,b; Hallett, 2007; George et al., 2007; Málly and Stone, 2007; Rossini and Rossi, 2007; Devlin and Watkins, 2007; Ridding and Rothwell, 2007). In addition, evidence has accumulated that demonstrates that TMS provides a valuable tool for *interventional neurophysiology applications*, modulating brain activity in a specific, distributed, cortico-subcortical network so as to induce controlled and controllable manipulations in behavior.

Repetitive transcranial magnetic stimulation (rTMS) has been found to be a promising noninvasive treatment for a variety of neuropsychiatric conditions (Devlin and Watkins, 2007; George et al., 2007; Aleman et al., 2007; Fregni and Pascual-Leone, 2007), and the number of applications continues to increase with a large number of ongoing clinical trials in a variety of diseases. Therapeutic utility of TMS has been claimed in the literature for psychiatric disorders, such as depression, acute mania, bipolar disorders, panic, hallucinations, obsessions/compulsions, schizophrenia, catatonia, post-traumatic stress disorder, or drug craving; neurologic diseases such as Parkinson's disease, dystonia, tics, stuttering, tinnitus, spasticity, or epilepsy; rehabilitation of aphasia or of hand function after stroke; and pain syndromes, such as neuropathic pain, visceral pain or migraine. A large industry-sponsored trial (O'Reardon et al., 2007) and a multi-center trial in Germany (Herwig et al., 2007) of rTMS in medication of refractory depression have been completed, and other appropriately controlled and sufficiently powered clinical trials of TMS are ongoing.

Most claims of therapeutic utility of TMS across conditions need further support and evidence-based clinical trial data, but the potential clinical significance is huge, affecting a large number of patients with debilitating conditions. A number of clinics have been set up worldwide offering TMS for treatment of various diseases, and rTMS is already approved by some countries for treatment of medication-refractory depression (i.e., Canada and Israel). In October 2008, a specific rTMS device was approved by the Food and Drug Administration in the United States for the treatment of patients with medication-refractory unipolar depression who have failed one good (but not more than one) pharmacological trial. It is reasonable to expect that the use of rTMS and its penetrance in the medical community will continue to increase across different medical specialties.

The number of laboratories using TMS for therapeutic or neuroscientific purposes, and consequently the number of healthy individuals and patients with various neurological or psychiatric diseases studied worldwide, has been increasing yearly for the past 20 years (Fig. 1). A further increase in the wide-spread use of TMS in medical therapeutic applications and research is expected. This makes the need for clear and updated safety guidelines and recommendations of proper practice of application critical.

Current safety precautions and practice recommendations remain guided by the consensus conference held at the National Institutes of Health in June 1996 and summarized in Clinical Neurophysiology (Wassermannn, 1998). These recommendations were adopted with minor modifications by the International Federation for Clinical Neurophysiology (Hallett et al., 1999). Ethical considerations on the application of TMS to health and disease were initially dealt with by Green et al. (1997) during the early stages of rTMS testing, and more recently have been addressed by several publications (Wolpe, 2002; Mashour et al., 2005; Illes et al., 2006; Steven and Pascual-Leone, 2006). However, as previously mentioned, the use of TMS has grown dramatically in the past decade, new protocols of TMS have been developed, changes in the devices have been implemented, TMS is being increasingly combined with other brain imaging and neurophysiologic techniques including fMRI and EEG, and a growing number of subjects and patients are being studied with expanding numbers of longer stimulation sessions.

The safety of TMS continues to be supported by recent meta-analyses of the published literature (see Machii et al., 2006; Loo et al., 2008; Janicak et al., 2008), yet there is a clear need to revisit the safety guidelines, update the recommendations of practice, and

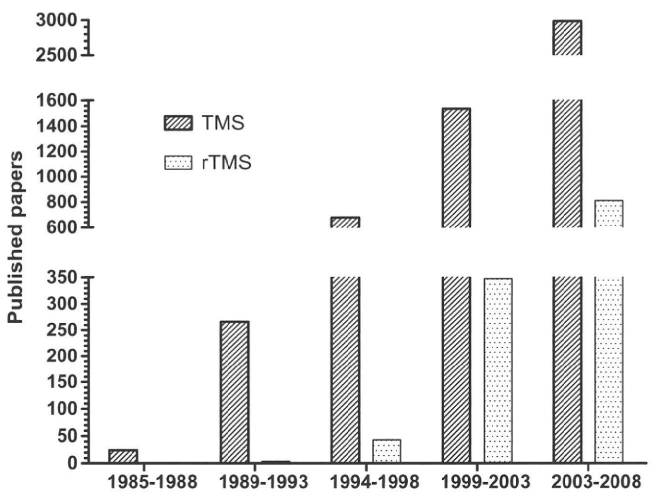

Fig. 1. Number of published papers per/year on Transcranial Magnetic Stimulation. Medline search updated to December 2008. Key words used are "Transcranial magnetic stimulation" (left bars) and "repetitive TMS" (right bars).

improve the discussion of ethical aspect to be reflective of the expanding uses of these powerful and promising techniques. Towards this end, a consensus conference took place in Certosa di Pontignano, Siena (Italy) on March 7–9, 2008. As in the 1996 NIH Consensus Conference, the 2008 meeting brought together some of the leading researchers in the fields of neurophysiology, neurology, cognitive neuroscience and psychiatry who are currently using TMS for research and clinical applications. In addition, representatives of all TMS equipment manufacturers were invited and those of Magstim, Nexstim, and Neuronetics were present, along with representatives from various regulatory agencies and several basic and applied scientists, including physicists, and clinicians whose work has bearing on decisions regarding the safe and ethical use of rTMS. The present article represents a summary of the issues discussed and the consensus reached. It follows the outline of the 1998 consensus statement, addressing all issues raised previously to provide corrections or updates where necessary, and including various new topics needed given technological advances.

2. Principles of TMS

2.1. Nomenclature

TMS can be applied one stimulus at a time, *single-pulse TMS*, in pairs of stimuli separated by a variable interval, *paired-pulse TMS*, or in trains, *repetitive TMS*. Single-pulse TMS can be used, for example, for mapping motor cortical outputs, studying central motor conduction time, and studying causal chronometry in brain-behavior relations. In paired pulse techniques TMS stimulation can be delivered to a single cortical target using the same coil or to two different brain regions using two different coils. Paired pulse techniques can provide measures of intracortical facilitation and inhibition, as well as study cortico–cortical interactions. Pairing can also be with a peripheral stimulus and a single TMS stimulus, paired associative stimulation (PAS).

When multiple stimuli of TMS are delivered in trains, one can differentiate "conventional" and "patterned" protocols of repetitive stimulation. For conventional protocols (Fig. 2), there is universal agreement that the term 'repetitive TMS' (rTMS) has replaced earlier uses of the terms 'rapid TMS' and 'rapid-rate TMS' and should be used to refer to the application of regularly repeated single TMS pulses. The term 'fast' or 'high-frequency' rTMS should be used to refer to stimulus rates of more than 1 Hz, and the term 'slow' or 'low-frequency' rTMS should be used to refer to stimulus rates of 1 Hz or less. Such a classification is based on the different physiological effects and degrees of risk associated with low- and high-frequency stimulation.

Patterned rTMS refers to repetitive application of short rTMS bursts at a high inner frequency interleaved by short pauses of no stimulation. Most used to date are the different theta burst (TBS) protocols in which short bursts of 50 Hz rTMS are repeated at a rate in the theta range (5 Hz) as a continuous (cTBS), or intermittent (iTBS) train (Huang et al., 2005; Di Lazzaro et al., 2008) (Fig. 2).

Lasting inhibitory aftereffects of 1 Hz rTMS and cTBS and facilitatory after-effects following high-frequency rTMS and iTBS were found on motor corticospinal output in healthy subjects, with a neurophysiologic substrate that remains unclear. Various mechanisms are worth considering, including synaptic changes resembling experimental long term depression (LTD) and long term potentiation (LTP) mechanisms, as well as shifts in network excitability, activation of feedback loops, activity-dependent

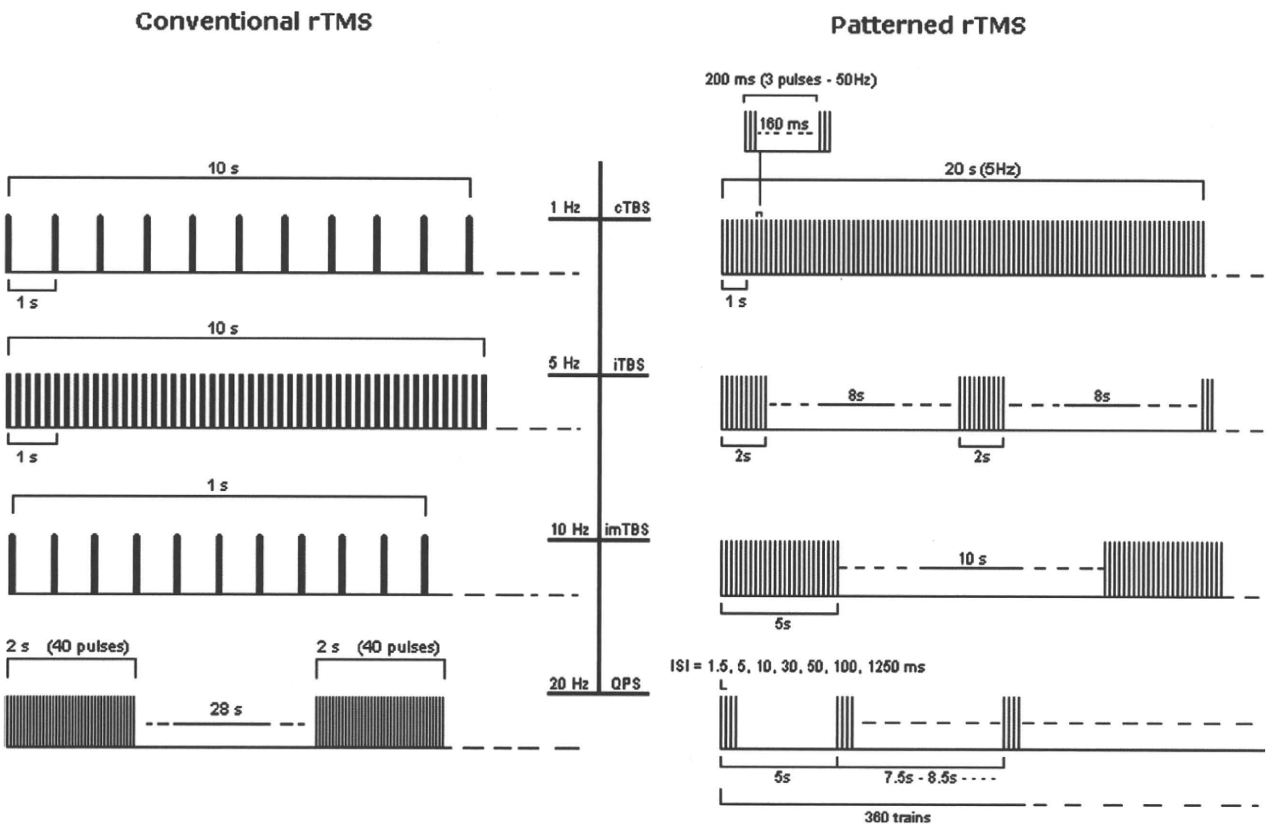

Fig. 2. Left panel (Conventional rTMS). From the top: examples of 10 s of rTMS at 1 Hz (first trace) and at 5 Hz (second trace); 1 s of rTMS at 10 Hz and a typical example of 20 Hz application for therapeutic purposes (trains of 2 s interleaved by a pause of 28 s). Right panel (Patterned rTMS). From the top: 20 s of continuous theta burst (first trace); intermittent theta burst (second trace) and intermediate theta burst (third trace). The fourth trace represents protocols of quadripulse stimulations (QPS).

metaplasticity (Gentner et al., 2008; Iezzi et al., 2008) etc. In the context of the present manuscript, a few issues are worth pointing out as they are relevant for the safety of TMS.

Regarding rhythmic, conventional repetitive, rTMS it is noteworthy, that in order to comply with present safety guidelines, protocols of slow rTMS ($\leqslant$1 Hz stimulation frequency) generally apply all pulses in a continuous train, whereas protocols of fast rTMS (e.g., $\geqslant$5 Hz stimulation frequency) apply shorter periods of rTMS separated by periods of no stimulation (e.g., 1200 pulses at 20 Hz and subthreshold stimulation intensity might be delivered as 30 trains of 40 pulses (2 s duration) separated by 28 s intertrain intervals (Fig. 2). There is only limited safety information on the effect of inserting pauses (intertrain intervals) into rTMS protocols (Chen et al., 1997). However, considering metaplasticity arguments (Abraham and Bear, 1996; Bear, 2003), it is likely that such pauses also have a significant impact on the effect of rTMS, both in terms of efficacy and safety. Therefore, further investigations are needed.

Regarding patterned rTMS, most TBS protocols employed to date replicate the original ones explored by Huang et al. (2005): for cTBS 3 pulses at 50 Hz are applied at 5 Hz for 20 s (300 total stimuli) or 40 s (600 stimuli). For iTBS twenty 2 s periods of cTBS each separated from the following by 8 s are applied (Fig. 2). Obviously, there are an infinite variety of combinations of such protocols, and it is important to emphasize that the effects and safety of the different protocols may differ, and that small changes, may have profound impact.

Recently, quadripulse stimulation (QPS) (Hamada et al., 2008) has been added to patterned rTMS procedures able to induce long-term changes of cortical excitability (see Fig. 2). Repeated trains of four monophasic pulses separated by interstimulus intervals of 1.5–1250 ms produced facilitation (at short intervals) or inhibition (at longer intervals), probably through a modulatory action on intracortical excitatory circuitry (Hamada et al., 2008).

The combination of repeated sub-motor threshold 5 Hz repetitive electrical stimulation of the right median nerve synchronized with sub-motor threshold 5 Hz rTMS of the left M1 at a constant interval for 2 min, or paired associated stimulation (PAS), is another protocol to temporally enhance rTMS effects at cortical level on the basis of a previously demonstrated interaction of the conditioning and test stimuli at the cortical level (Mariorenzi et al., 1991), perhaps through (meta)-plasticity mechanisms (Quartarone et al., 2006).

Repetitive paired-pulse stimulation (not included in Fig. 2) has be performed at ICF periodicity (Sommer et al., 2001) or i-wave periodicity (Di Lazzaro et al., 2007) [(also termed iTMS (Thickbroom et al., 2006) or rTMS (Hamada et al., 2007)]. Although higher excitability increases could be observed in comparison to single-pulse rTMS no seizures have been reported so far with this technique.

In all studies introducing new TMS protocols, safety should be addressed by including careful monitoring of motor, sensory and cognitive functions before, during, and after the intervention.

2.2. Interaction of magnetic field with tissue

In TMS, electric charge stored in a capacitor is discharged through a stimulation coil, producing a current pulse in the circuit that generates a magnetic field pulse in the vicinity of the coil. According to Faraday's law of electromagnetic induction, this time-varying magnetic field induces an electric field whose magnitude is proportional to the time rate of change of the magnetic field, which in the case of TMS is determined by the rate of change of the current in the coil. If the coil is held over a subject's head, the magnetic field penetrates scalp and skull, and induces an electric field in the brain. The induced electric field causes ions to flow in the brain, without the need for current to flow across the skull and without charged particles being injected into the scalp. In contrast, in transcranial electric stimulation (TES) charge is injected into the scalp at the electrodes and current must flow through the skull. Due to the low conductivity of the skull, in TES a large potential difference must be applied between the electrodes in order to achieve a current density in the brain high enough to stimulate neurons, and this leads to a much higher current density in the scalp. Thus, the ratio of the maximum current density in the scalp to the maximum current density in the brain is much lower in TMS than for TES, allowing TMS to stimulate cortical neurons without the pain associated with TES.

The flow of ions brought about by the electric field induced in the brain alters the electric charge stored on both sides of cell membranes, depolarizing or hyperpolarizing neurons. The existence of passive ion channels renders the membrane permeable to these ions: an increased membrane conductance decreases the amplitude of the change in membrane potential due to the induced electric field and decreases the time constant that characterizes the leakage of the induced charge. Experimental evidence (Amassian et al., 1992; Maccabee et al., 1993) and theoretical calculations (Nagarajan et al., 1993) indicate that stimulation occurs at a lower threshold where axons terminate, or bend sharply, in the relatively uniform electric field induced by the TMS stimulation coil. Accordingly, stimulation should occur where the electric field is strongest and points along the direction of an axon that terminates, for example at a synapse, or bends sharply. Axons with larger length constants, and hence larger diameters, are expected to be stimulated at lower stimulus intensity.

The stimulators and coils currently in production develop about 1.5–2.0 Tesla (T) at the face of the coil, produce currents changing at rates up to 170 A/μs (Thielscher and Kammer, 2002) and induce electric fields in the cortex of up to about 150 V/m. They are thought, depending by the stimulation intensity, to be able to activate cortical neurons at a depth of 1.5–3.0 cm beneath the scalp using standard Figure 8, circular or double-cone coils. The Figure 8 coil produces a more focal and shallower stimulation, whereas the double-cone coil was especially designed for stimulation of deeper cortical targets. When using intensities below 120% of motor threshold, the stimulation can not induce direct activation at depth of more than 2 cm beneath the scalp (Roth et al., 2002, 2007; Zangen et al., 2005; Roth et al.,).

Stimulus waveform and current direction have a significant impact on stimulation threshold. Shorter stimulus duration requires larger pulse amplitude but lower pulse energy to achieve stimulation (Barker, 1991; Hsu et al., 2003; Peterchev et al., 2008). For monophasic pulses over the motor cortex, a lower threshold is observed when the induced current flows in the brain in posterior-anterior direction. For biphasic pulses, the threshold is lowest when the induced current flows in the posterior-anterior direction in the second phase, and hence in the opposite direction from the first phase (Kammer et al., 2001). This effect can be explained in terms of the delayed (capacitive) response of the membrane (Davey and Epstein, 2000; Corthout et al., 2001). Stimulation threshold is lower for biphasic stimuli than for monophasic stimuli only if compared in terms of the energy stored in the stimulator's capacitors. In practice, the relative value of these two thresholds may be different for different stimulators (Kammer et al., 2001), which might have relevance in terms of safety.

Several simulation models have been developed to provide a view of the electromagnetic field distributions generated in biological tissue during TMS (Wagner et al., 2007). The simplified geometries of early models argued for the absence of currents normal to the superficial cortex and limited effects of surrounding tissues or altered anatomies, but more realistic head models indicate that such conclusions are inaccurate. For example, the conjecture that radial currents are absent during TMS, has influenced the

interpretation of clinical studies related to the generation of indirect (I) and direct (D) waves and justified the claim that inter-neurons tangential to the cortical surface are preferentially stimulated. However, such clinical interpretations need to be reevaluated in light of recent modeling work (Nadeem et al., 2003; Miranda et al., 2003; Wagner et al., 2004; De Lucia et al., 2007) that clearly demonstrate the importance of accounting for the actual head model geometry, tissue compartmentalization, tissue conductivity, permittivity, heterogeneity and anisotropy when calculating the induced electric field and current density. From a safety point of view, it is important to note that changes in the tissue anatomy and electromagnetic properties have been shown to alter the TMS induced stimulating currents in both phantom and modeling studies. Wagner et al. (2006, 2008) compared the TMS field distributions in the healthy head models with those in the presence of a stroke, atrophy or tumor. For each of these pathologies, the TMS induced currents were significantly altered for stimulation proximal to the pathological tissue alterations. The current density distributions were modified in magnitude and direction, potentially altering the population of stimulated neural elements. The main reason for this perturbation is that altered brain tissue can modify the conductivities and effectively provide paths of altered resistance along which the stimulating currents flow. Given these findings, modeling of induced electric field and current density in each patient with brain pathologies using a realistic head model, would be desirable to maximize precision. However, it is important to emphasize, that even in the absence of individualized modeling of induced currents, studies of TMS in a variety of patient populations over the past decades have proven remarkably safe if appropriate guidelines are followed.

2.3. Types of coils

The most commonly used coil shape in TMS studies consists of two adjacent wings, and is termed the Figure 8. This shape allows relatively focal stimulation of superficial cortical regions, underneath the central segment of the Figure 8 coil. Neuronal fibers within this region with the highest probability for being stimulated are those which are oriented parallel to the central segment of the coil (Basser and Roth, 1991; Roth and Basser, 1990; Chen et al., 2003).

The relative angle between the wings affects the efficiency and focality of the coil. Coil elements which are non-tangential to the scalp induce accumulation of surface charge, which reduces coil efficiency (Tofts, 1990; Branston and Tofts, 1991; Eaton, 1992). Hence, when the angle is smaller than 180°, the wings are more tangential to the scalp, and the efficiency increases (Thielscher and Kammer, 2004). Yet, a one-plane design (180° head angle) is the most convenient form for fine localization over the head; hence it is the most commonly used.

Many studies are performed with circular coils of various sizes. Larger diameters allow direct stimulation of deeper brain regions, but are less focal. While no comparative studies have been performed to analyze the safety of circular vs. Figure 8 coils, there is no evidence for large differences in the safety parameters.

The double cone coil is formed of two large adjacent circular wings at an angle of 95°. This large coil induces a stronger and less focal electric field relative to a Figure 8 coil (Lontis et al., 2006), and allows direct stimulation of deeper brain regions. Because of its deep penetration, this coil allows for activation of the pelvic floor and lower limbs motor representation at the interhemispheric fissure. It is also used for cerebellar stimulation. It may induce some discomfort when higher intensities are required for stimulation of deep brain regions.

A more recent development allowing considerable reduction in power consumption and heat generation during operation, makes use of ferromagnetic cores (Epstein and Davey, 2002). The safety of such iron-core coils, using a relatively high intensity (120% of MT) and frequency (10 Hz, 4 s trains), was recently demonstrated in a large multi-center study evaluating its antidepressant effects (O'Reardon et al., 2007).

Overheating of coils during rTMS poses severe limitations on effective and safe operation, and requires an adequate cooling method. Weyh et al. (2005) introduced a Figure 8 coil with a reduced-resistance design to achieve significantly improved thermal characteristics. In addition to having increased electrical efficiency, iron-core coils offer advantages in this regard as well, as the ferromagnetic core serves as a heat sink. Water-, oil- and forced-air cooling methods have been implemented by various manufacturers.

Coil designs for stimulation of deeper brain areas, termed H-coils, have been tested *ex vivo* and in human subjects (Roth et al., 2002, 2007; Zangen et al., 2005), Other theoretical designs for deep brain TMS have been evaluated with computer simulations, such as stretched C-core coil (Davey and Riehl, 2006; Deng et al., 2008) and circular crown coil (Deng et al., 2008). Coils for deep brain stimulation have larger dimensions than conventional coils, and provide a significantly slower decay rate of the electric field with distance, at the expense of reduced focality. Due to their reduced attenuation of the electric field in depth, these coils could be suitable for relatively non-focal stimulation of deeper brain structures. However, it is important to remember that as in all TMS coils, the stimulation intensity is always maximal at the surface of the brain. The safety and cognitive effects of some H-coils at relatively high intensity (120% MT) and frequency (20 Hz) have been assessed (Levkovitz et al., 2007), and these coils have received regulatory approval for human use in Europe.

3. Safety concerns

3.1. Heating

Tissue heating of the brain by a single-pulse TMS itself is very small and is estimated to be definitely less than 0.1 °C (Ruohonen and Ilmoniemi, 2002). It appears to be even smaller in areas with low perfusion such as cysts or strokes (R. Ilmoniemi, personal communication). However, high brain blood perfusion ensures a safety range (Brix et al., 2002). For comparison, heating in the immediate surround of deep brain stimulation electrodes is estimated to be at maximum 0.8 °C (Elwassif et al., 2006).

Eddy currents induced in conductive surface electrodes and implants can cause them to heat up (Roth et al., 1992; Rotenberg et al., 2007). The temperature increase depends on the shape, size, orientation, conductivity, and surrounding tissue properties of the electrode or implant as well as the TMS coil type, position, and stimulation parameters. Silver and gold electrodes are highly conductive and can heat excessively, potentially causing skin burns. Temperature of 50 °C for 100 s or 55 °C for 10 s can produce skin burns (Roth et al., 1992). The use of low-conductivity plastic electrodes can reduce heating. Radial notching of electrodes and skull plates can also reduce heating by interrupting the eddy current path. Skull plates made of titanium tend to have low heating, due to the low conductivity of titanium and radial notching (Rotenberg et al., 2007). Brain implants such as aneurysm clips and stimulation electrodes can heat as well. Brain tissue heating above 43 °C can result in irreversible damage (Matsumi et al., 1994). If TMS is to be applied near electrodes or implants, it is advisable to first measure the heating *ex vivo* with the parameters specified in the planned TMS protocol. The results of such testing should be reported for the benefit of the scientific community.

3.2. Forces and magnetization

The magnetic field pulse generated by the TMS coil exerts attractive forces on ferromagnetic objects and repulsive forces on non-ferromagnetic conductors. Therefore, TMS can result in forces on some head implants that could potentially displace them. The forces on ferromagnetic objects tend to be larger than those on non-ferromagnetic conductors. Titanium skull plates are non-ferromagnetic and low-conductivity, and may have radial notches which reduce the induced force. Some titanium skull plates may be safe for TMS (Rotenberg et al., 2007).

The net energy imparted to stainless steel aneurysm clips is measured to be typically less than 10^{-10} J, equivalent to the clip being moved vertically by less than 0.0003 mm, which is unlikely to produce a clinical problem (Barker, 1991). Cochlear implants incorporate a magnet under the scalp that could be moved or demagnetized by the TMS pulse. Analogously to the evaluation of heating, it is advisable to first measure the forces *ex vivo* with the parameters specified in the planned TMS protocol. Jewelry, glasses, watches and other potentially conducting or magnetic objects worn on the head should be removed during TMS to prevent interactions with the magnetic field.

3.3. Induced voltages

The strong magnetic field pulse emitted by the TMS coil can induce large voltages in nearby wires and electronic devices. The wires connecting to scalp electrodes should be kept free of loops and should be twisted together to reduce magnetically-induced voltages. Active brain implants, such as deep brain stimulation (DBS) systems, epidural electrode arrays for cortical stimulation, and cochlear implants contain intracranial electrodes connected to subcutaneous wires in the scalp. TMS can induce voltages in the electrode wires whether the implant is turned ON or OFF, and this can result in unintended stimulation in the brain. TMS pulses can also damage the internal circuitry of electronic implants near the coil, causing them to malfunction.

More in detail, three *ex vivo* studies have specifically dealt with the issue of safety (Kumar et al., 1999; Kühn et al., 2004; Schrader et al., 2005). Kumar et al. (1999) investigated the safety of TMS applied to non-implanted deep brain electrodes embedded in a conducting gel with impedance similar to the impedances found when the electrodes are in the brain. They found that the induced currents in the leads are 20 times smaller than those normally produced by the stimulator when it is used in patients, and concluded that magnetic stimulation over the coiled scalp leads does not deliver damaging stimuli to the patient's brain (Kumar et al., 1999). As a part of a study of modulation of motor cortex excitability by DBS, Kühn et al. (2004) tested the voltages induced in DBS leads in a phantom skull with methods similar to Kumar et al. (1999). They reported voltages up to 0.7 V induced in the electrode wires, and concluded that these are safe levels, since they are below the voltages generated by DBS. Schrader et al. (2005) assessed the effects of single-pulse TMS on a vagal nerve stimulation (VNS) device in regard to any current induced in VNS leads during TMS. They concluded that single-pulse TMS can be safely applied to individuals who have an implanted VNS device.

A significant limitation of the *ex vivo* safety studies (Kumar et al., 1999; Kühn et al., 2004; Schrader et al., 2005) is that only the induced voltages between pairs of contacts on the electrode lead were tested, whereas the induced voltages between the electrode contacts and the contact formed by the implanted pulse generator (IPG) case were not measured. The circuit formed by the wires connecting pairs of electrode contacts constitutes a conductive loop with a relatively small area, thus electromagnetic induction produces low voltages. On the other hand, the circuit formed by the wires connecting to the electrode contacts and the IPG case constitutes a conductive loop with a significantly larger area, and therefore electromagnetic induction can produce relatively high voltages. Thus, the induced voltages and currents reported in existing *ex vivo* safety studies could be significantly underestimating the magnitudes induced *in vivo*.

In addition to voltages and currents induced in the stimulation leads, the electromagnetic pulse generated by TMS can cause malfunction or even damage in the internal circuitry of electronic implants near the TMS coil. TMS pulses delivered *ex vivo* at a distance of 2–10 cm from the TMS coil to DBS IPG caused the IPG to malfunction, and for distances of less than 2 cm, the IPG was permanently damaged (Kumar et al., 1999; Kühn et al., 2004). A similar study of the effect of TMS pulses on a VNS IPG did not detect signs of malfunction or damage to the IPG by the TMS pulse (Schrader et al., 2005).

Cochlear implants consist of a loop antenna, a permanent magnet, an electronic chip implanted under the scalp, and an electrode implanted in the cochlea. There is no safety data on TMS in subjects with cochlear implants, but basic physics considerations suggest that it is likely unsafe. The TMS pulse can induce high voltages in the loop antenna, can move or demagnetize the permanent magnet, and can cause malfunction or damage to the electronic chip. Further, cochlear implants are not MRI compatible. Therefore, TMS should not be performed in subjects with cochlear implants, unless a detailed safety evaluation proves there are no adverse effects.

3.4. TMS in patients with implanted stimulating/recording electrodes

A large number of TMS studies have been performed in patients with electrodes implanted both in central and peripheral nervous system. Most employed single-pulse TMS, some used paired pulse TMS and a few studies used repetitive TMS (see Supplemental material, Table S1). The main aims of such studies have been:

(a) Evaluation of the effects of TMS on the central nervous system activity either by recording the responses evoked by TMS or by evaluating the changes of the ongoing spontaneous electrophysiological activity after TMS through the implanted electrodes;
(b) Evaluation of the effects of stimulation of nervous system structures by the implanted electrodes, as revealed by TMS evoked responses.

The first *in vivo* study with spinal cord stimulators was performed by Kofler et al. (1991) in four patients, and they reported that TMS was safely applied with the devices turned OFF and ON, with no apparent adverse effect (Kofler et al., 1991). Since then, studies performed in patients with implanted electrodes (see Supplemental material, Table S1) have used mainly three types of electrodes: (1) epidural electrodes (implanted over the cerebral cortex or spinal cord); (2) deep brain electrodes; or (3) peripheral or cranial nerve stimulating electrodes (e.g., vagus nerve (VN) electrodes). Some of the studies were performed in the few days following implantation, whilst the electrode leads were externalized before connection to a subcutaneous stimulus generator, while other studies were performed in patients with the leads connected to implanted stimulators. Two of the latter studies (Kühn et al., 2002; Hidding et al. 2006) showed that TMS-induced lead currents can produce motor responses *in vivo*, suggesting that the magnitude of these currents was higher than the negligible levels measured *ex vivo*. This phenomenon could be explained by currents induced between the electrode contacts and the IPG case, which were not measured in the *ex vivo* tests (see Section 3.3). Kühn et al. (2002) performed TMS in 5 dystonic patients with implanted electrodes in globus pallidus

internus. These authors suggested that TMS can induce currents in the subcutaneous wire loops in patients with implanted DBS electrodes which are sufficient to activate corticospinal fibres subcortically and to elicit pseudo-ipsilateral hand motor responses (Kühn et al., 2002). Similar findings were reported in 8 parkinsonian patients with subthalamic nucleus (STN) electrodes and leads connected to an implanted stimulator (Hidding et al., 2006). The mean onset latencies of motor responses recorded in the relaxed first dorsal interosseous muscle were significantly shorter after electrode implantation compared to the preoperative state. The authors ascribed the shortening of the corticomotor conduction time to inadvertent stimulation of fast-conducting descending neural elements in the vicinity of the STN through current induction in subcutaneous scalp leads underneath the TMS coil connecting the external stimulator with STN electrodes, thereby producing submotor threshold descending volleys. Importantly though, no adverse effects were reported by Kühn et al. (2002) and by Hidding et al. (2006).

In summary, based on *ex vivo* and *in vivo* studies, it appears that TMS can be safely applied to patients who have implanted stimulators of the central and peripheral nervous system when the TMS coil is not in close proximity to the internal pulse generator (IPG) system. However, we lack detailed information as to what constitutes a safe distance between the TMS coil and the implanted stimulator, and how coil shape, coil angulation, etc. influence this relation. Therefore, TMS should only be done in patients with implanted stimulators if there are scientifically or medically compelling reasons justifying it. TMS procedures need to strictly follow a pre-specified experimental protocol and setting, with appropriate oversight by the Institutional Review Board or Ethic Committee. In such instances, to prevent accidental firing of the TMS coil near electronic implants, the subjects could wear a lifejacket or a similar arrangement which provides about 10 cm of padding around the electronic implant (Schrader et al., 2005).

TMS is considered safe in individuals with VNS systems (Schrader et al., 2005), cardiac pacemakers, and spinal cord stimulators as long as the TMS coil is not activated near the components located in the neck or chest. If a TMS coil is discharged close to the implanted wires connecting the electrodes to the IPG, potentially significant voltages and currents could be induced between the electrode leads and the IPG, which could cause unintended neural stimulation and may present a safety risk. This scenario can occur in DBS and cortical stimulation with epidural electrodes. Additional safety studies should be conducted to evaluate the magnitude of the voltages and currents induced in implanted stimulation systems. Finally, TMS in subjects with cochlear implants should not be performed, due to multiple possibly unsafe interactions between the TMS pulse and the implant.

3.5. Magnetic field exposure for subjects/patients

Single sessions of TMS or rTMS do not carry the risk of significant magnetic field exposure since the total time is too short. However, a typical treatment course of rTMS for a psychiatric application (e.g., 10 Hz, trains of 20 pulses, 5× s, 20 sessions) yields about 5 s of total exposure (Loo et al., 2008). Theoretically, this kind of exposure would fall into radiofrequency range (i.e., from 3 kHz to 300 GHz), assuming a continuous stimulation with each pulse lasting about 250 μs (Barker, 1991).

In a current TMS depression trial, the researchers (M. George, personal communication) are delivering 6000 stimuli in a day (120% of MT, 10 Hz, 5 s on-10 off, for 30 min each day), in an open-ended dynamically adaptive design where they treat to remission as long as there is continued improvement. There is a maintenance phase and patients can be retreated if they relapse. One 28-year old patient has now received 70 sessions over 12 months, or 420.000 pulses, with no side effects. Several patients with amyotrophic lateral sclerosis have also received a very prolonged treatment using cTBS. One 75-year old patient has received 130 sessions over 26 months with a total number of 156,000 stimuli, while 7 patients received 60 sessions over 12 months with a total number of 72,000 stimuli (Di Lazzaro et al., 2009).

As pointed out (Loo et al., 2008), it is unclear whether the high intensity, pulsed stimulation of TMS has the same long-term effects of continuous, low-intensity, occupational exposure. It is even less clear whether effects of long-term exposure to rTMS might be changed by concurrent medications. Prospective studies in this sense would be desirable. Nonetheless, it is worth noting that chronic exposure to electro-magnetic fields appears safe at levels even greater than those possible with TMS (Gandhi, 2002; Martens, 2007).

3.6. Magnetic field exposure for operators

Safety issues are rarely addressed for operators who are exposed to magnetic field several hours every day for years by performing TMS. Guidelines for occupational levels of exposure to electromagnetic fields have been proposed by the International Commission on Non-Ionizing Radiation Protection (see ICNIRP, 2003) and by a Directive from the European Parliament [directive 2004/40/EC (Riches et al., 2007a)]. This directive introduces Exposure Limit Values for workers and also Action Values (magnitude of electromagnetic field which is directly measurable). In contrast, long term effects have been excluded from the scope of the directive. This directive has been operational from 30 April 2008 in all countries of the European Union (now postponed to April 30, 2012). Occupational exposure to magnetic fields has been measured for MRI units (Riches et al., 2007a). Exposure values are 100 times below the recommended exposure limits (Bradley et al., 2007), except in case of interventional procedures (Hill et al., 2005; Riches et al., 2007b).

Regarding TMS/rTMS, only one study has been performed using the MagPro machine (Medtronic), MC-B70 Figure 8 coil, 5 Hz frequency, and stimulus intensity of 60–80% stimulator output (Karlström et al., 2006). In these conditions, worker's exposure limits for the magnetic field pulses are transgressed at a distances of about 0.7 m from the surface of the coil. This single observation makes necessary further research to confirm it and to determine the limiting distance to the coil according to the type of TMS machine, the type of coil, the frequency/intensity of stimulation and the total exposure time.

The potential risk of long-term adverse event for rTMS operators due to daily close exposure (even to weak electromagnetic fields), repeated for years, is an open issue that should be addressed in the future.

4. Side effects

All the known side effects linked with TMS use are summarized in Table 1. It is apparent that data on theta burst stimulation (TBS) are still not sufficient to claim or deny safety hazards. This implies that future therapeutic and research studies employing TBS and other forms of patterned repetitive TMS should explicitly address this issue, which has been neglected up to now. Below, the most significant, potential side effects of conventional TMS are commented on in further detail, including potentially hazardous TMS-related activity (see points 3.1–3.8):

4.1. Hearing

Rapid mechanical deformation of the TMS stimulating coil when it is energized produces an intense, broadband acoustic artifact that may exceed 140 dB of sound pressure level (Counter and

Table 1
Potential side effects of TMS. Consensus has been reached for this table.

Side effect	Single-pulse TMS	Paired-pulse TMS	Low frequency rTMS	High frequency rTMS	Theta burst
Seizure induction	Rare	Not reported	Rare (usually protective effect)	Possible (1.4% crude risk estimate in epileptic patients; less than 1% in normals)	Possible (one seizure in a normal subject during cTBS) (see para 3.3.3)
Transient acute hypomania induction	No	No	Rare	Possible following left prefrontal stimulation	Not reported
Syncope	Possible as epiphenomenon (i.e., not related to direct brain effect)				Possible
Transient headache, local pain, neck pain, toothache, paresthesia	Possible	Likely possible, but not reported/ addressed	Frequent (see para. 3.3)	Frequent (see para. 3.3)	Possible
Transient hearing changes	Possible	Likely possible, but not reported	Possible	Possible	Not reported
Transient cognitive/ neuropsychologial changes	Not reported	No reported	Overall negligible (see Section 4.6)	Overall negligible (see Section 4.6)	Transient impairment of working memory
Burns from scalp electrodes	No	No	Not reported	Occasionally reported	Not reported, but likely possible
Induced currents in electrical circuits	Theoretically possible, but described malfunction only if TMS is delivered in close proximity with the electric device (pace-makers, brain stimulators, pumps, intracardiac lines, cochlear implants)				
Structural brain changes	Not reported	Nor reported	Inconsistent	Inconsistent	Not reported
Histotoxicity	No	No	Inconsistent	Inconsistent	Not reported
Other biological transient effects	Not reported	Not reported	Not reported	Transient hormone (TSH), and blood lactate levels changes	Not reported

Borg, 1992). This exceeds the recommended safety levels for the auditory system (OSHA). Before using a given coil/stimulator, the operator may consult the manufacturer's Instructions for use or technical specifications to check the specified sound pressure levels.

After exposure to the TMS stimulus, a small proportion of adult humans have experienced transient increases in auditory thresholds (Pascual-Leone et al., 1992; Loo et al., 2001). Permanent threshold shift has been observed in a single individual who did not have ear plugs and was being stimulated with an H-coil (Zangen et al., 2005). The majority of studies in which hearing protection was used report no change in hearing after TMS (Pascual-Leone et al., 1991; Levkovitz et al., 2007; Folmer et al., 2006; Rossi et al., 2007a; Janicak et al., 2008). The single publication regarding hearing safety in pediatric cases reports no change in hearing in a group of 18 children without hearing protection (Collado-Corona et al., 2001). This is encouraging; however, the sample size is too small to ensure hearing safety for pediatric cases. Young children are of particular concern because their canal resonance is different from adults, their smaller head size results in the TMS coil being closer to the ear, and appropriate hearing protection devices for children are not available.

Therefore, it is recommended that:

(1) Hearing safety concerns for adults be addressed by: (i) use of approved hearing protection (earplugs or ear muffs) by individuals trained in placement of these devices; (ii) prompt referral for auditory assessment of all individuals who complain of hearing loss, tinnitus, or aural fullness following completion of TMS; (iii) those with known pre-existing noise induced hearing loss or concurrent treatment with ototoxic medications (Aminoglycosides, Cisplatine) should receive TMS only in cases of a favorable risk/benefit ratio, as when rTMS is used for treatment of tinnitus.
(2) Individuals with cochlear implants should not receive TMS (see also paragraphs 2.2 and 2.3).
(3) The acoustic output of newly developed coils should be evaluated and hearing safety studies should be conducted as indicated by these measures.
(4) Hearing safety concerns for children have not been sufficiently addressed in published literature (see also paragraph 4.5) to justify participation by pediatric healthy volunteers in TMS studies until more safety data are available. Application of rTMS in pediatric patient populations with therapeutic intent may be reasonable if the potential benefits outweigh the theoretical risks of hearing problems.

4.2. EEG aftereffects

Recording of electroencephalographic (EEG) activity immediately before, during, and after TMS is possible provided that certain technical challenges are addressed and few precautions taken (Ilmoniemi et al., 1997; Bonato et al., 2006; Thut et al., 2005; Ives et al., 2006; Morbidi et al., 2007). Problems related to the saturation of the EEG recording amplifiers from the TMS pulse have been overcome via artifact subtraction, pin-and-hold circuits, the use of modified electrodes which do not transiently change their shape due to the stimulus impact, and altering the slew rate of the preamplifiers.

There is a considerable number of publications of combined TMS-EEG to date (85 studies on more than 1000 volunteers over the last 19 years). The studies that quantified aftereffects on EEG activity induced by conventional or patterned rTMS are listed in Table S2 (supplemantal material) and discussed in this section. The studies on EEG-aftereffects in the form of potential TMS-induced epileptiform EEG-abnormalities are listed in Table 2 and discussed in Section 4.3.5. Single-pulse studies are not included in either table since safety concerns did not arise. However, in Table 2, special emphasis is placed on patient populations who might be more vulnerable to TMS due to several factors (i.e., brain damage, drug treatment or discontinuation of treatment for the purpose of a study).

Table 2
Inspection of EEG for epileptiform abnormalities during or after repetitive TMS in patients and healthy subjects. Consensus has been reached for this table.

Authors	Subjects	TMS-parameters	EEG-measures	Timing of EEG	Findings with potential safety concern	Duration of after-effects
Loo et al., 2001	N = 18 Depression	10 days of 10 Hz/30 × 5 s train: 25 s ITI DLPFC/110%MT	visual inspection waking EEG	before and after TMS	**Yes:** Minor, potentially epileptiform abnormalities in 1 patient (in the absence of seizure)	*not assessed*
Boutros et al., 2001	N = 5 Depression	max 10 days of 5–20 Hz/max 20 × 2 s: 58 s ITI DLPFC/80–100%MT	visual inspection waking EEG	before and during TMS	**No:** despite EEG-abnormalities at baseline: no change	
Boutros et al. (2000)	N = 14 Depression	10 days of 20 Hz/20 × 2 s train: 58 s ITI DLPFC/80%MT	visual inspection waking EEG	before, during and after TMS	**Yes:** 1 case with rare slow-wave transients online to TMS	no after-effects
	N = 7 Schizophrenia	4 sessions of 1 Hz/4 :6 :12 :16 min temporal cortex	visual inspection waking EEG	before, during and after tTMS	**No** (no change)	no after-effects
	N = 5 OCD	5 days of 20 Hz/30 × 2 s train: 58 s ITI DLPFC/80%MT	visual inspection waking EEG	before, during and after TMS	**Yes:** 1 case with increased theta activity during TMS	no after-effects
Fregni et al., 2006	N = 15 Stroke	5 days of 1 Hz/20 min Unaffected hemisphere/ 100%MT	visual inspection waking EEG	online and 2 h after treatment	**No** (no change)	no after-effects
Cantello et al., 2007	N = 43 Epilepsy	5 days of 0.3 Hz/55.5 min vertex/100%rMT	visual inspection waking EEG Semi-quantitative	before and after TMS	**No:** decrease in interictal spikes in 1/3 of patients	
Joo et al., 2007	N = 35 Epilepsy	5 days of 0.5 Hz/50-100 min focus or vertex/100%rMT	visual inspection waking EEG	before and after treatment	**No:** decrease in interictal spikes	*not assessed*
Conte et al., 2007	N = 1 Epilepsy	different sessions of 5 Hz/2 s trains vertex/120%MT	duration of spike and waves	online to TMS	**No:** decrease in duration of discharges	no after-effect
Fregni et al., 2006	N = 21 Epilepsy	5 days of 1 Hz/20 min foucs/70% max	visual inspection waking EEG	before and after TMS	**No:** decrease in epileptiform discharges	up to 30 days washed out at 60 days
Fregni et al., 2005	N = 8 Epilepsy	1 session of 0.5 Hz/20 min Focus/65% max	visual inspection waking EEG	before and after treatment	**No:** decrease in epileptiform discharges	at least 30 days
Misawa et al., 2005	N = 1 Epilepsy	1 session of 0.5 Hz/3.3 min focus/90%MT	visual inspection waking EEG	during TMS	**No:** significant change in EEG with epilepsy abolishment	2 month
Rossi et al., 2004	N = 1 Epilepsy	1 session of 1 Hz/10 min focus/90%rMT	Spike averaging	before and after TMS	**No:** reduction in spike amplitude	*not assessed*
Menkes and Gruenthal, 2000	N = 1 Epilepsy	4 × 2 days of 0.5 Hz/3.3 min focus/95%MT	visual inspection waking EEG	before and after TMS	**No:** reduction in interictal spikes	*not assessed*
Schulze-Bonhage et al., 1999	N = 21 Epilepsy	4 stimuli at 20/50//100/500 Hz M1/120–150%MT	visual inspection waking EEG	during TMS	**No:** no case of after-discharges clearly assignable to TMS/ interictal activity unchanged	no after-effects
Jennum et al., 1994	N = 10 Epilepsy	1 session of 30 Hz/8 × 1 s trains: 60 s ITI temporal and frontal/120%MT 50 Hz/2×1 s train: 60 s ITI frontal/120%MT	visual inspection waking EEG	before, during and after tTMS	**No:** less epileptiform activity during TMS **No:** less epileptiform activity during TMS	recovery after 10 min Recovery after 10 min
Steinhoff et al., 1993	N = 19 Epilepsy	0.3–0.1 Hz	visual inspection waking EEG			**No:** reduction of epileptic activity in some cases
Hufnagel and Elger (1991)	N = 48 Epilepsy	single or low frequency (<0.3 Hz)	visual inspection subdural electrodes		**Yes/no:** enhancement and suppression of epileptiform activity	na
Dhuna et al., 1991	N = 8 Epilepsy	1 session of 8–25 Hz Various sites/intensities	visual inspection waking EEG		**No:** 7 patients: no EEG changes Yes: 1 patient: seizure induction with 100% output intensity	no after-effects
Kanno et al., 2001	N = 1 Patient	1 session 0.25 Hz/2 × 3.3 min train DLPFC/110%MT	visual inspection waking EEG	during TMS	**Yes:** Potential epileptiform activity (focal slow-wave, no seizure)	no after-effects
Huber et al., 2007	N = 10 healthy	5 session of 5 Hz/6 × 10 s train: 5 s ITI M1/90%rMT	visual inspection waking EEG	during TMS	**No** (no abnormalities)	no after-effects
Jahanshahi et al., 1997	N = 6 healthy	2 sessions of 20 Hz/50 × 0.2 s: 3 s ITI	visual inspection waking EEG	before and after TMS	**No** (no abnormalities)	no after-effects

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