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Electroencephalography and clinical Neurophysiology 105 (1997) 422–429

Rapid rate transcranial magnetic stimulation – a safety study

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Accepted for publication: 24 July 1997

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Abstract

We assessed the safety of repeated short trains (4 stimuli) of rapid-rate transcranial magnetic stimulation (rrTMS) over the left motor cortex in 6 healthy normal subjects. rrTMS involved two separate blocks of 50 consecutive trains of 4 stimuli at a frequency of 20 Hz and an intensity of 5–10% above active motor threshold. We monitored EEG, and assessed aspects of neurological (balance, gait, two-point discrimination, blood pressure, pulse rate), cognitive (attention, memory, executive function) and motor function (speed of movement initiation and execution and manual dexterity) before and after the two blocks of rrTMS. EMG was also recorded from a number of hand, forearm and arm muscles contralateral to the site of stimulation. Two blocks of repeated rrTMS at 20 Hz and 5–10% above active motor threshold did not produce any adverse effects. Measures of neurological, cognitive and motor function showed no change following rrTMS. From the EMG recording there was evidence of increase in the amplitude of the motor evoked potentials (MEPs) recorded from the biceps in one subject during the first block of rrTMS, but this did not occur in the second block. A similar magnification of MEPs was also observed in another subject only during the second block of stimulation. When applied using parameters falling within published guidelines (Pascual-Leone et al., 1993; Pascual-Leone et al., 1994), repeated rrTMS is a relatively safe technique in healthy normal subjects. As rrTMS allows disruption of cortical function for a longer period, it has the potential of becoming a particularly useful tool for the study of cognitive function as well as sensory or motor function. © 1997 Elsevier Science Ireland Ltd.

Keywords: Rapid rate magnetic stimulation; Safety study

1. Introduction

Transcranial magnetic stimulation (TMS) is a recent technique which allows painless stimulation of the brain through the scalp of normal conscious subjects. It was first described by Barker et al. (1985) and since then has become a routine clinical and research tool. In the majority of studies, single stimuli have been applied to the motor cortex at intervals of 2 s or more in order to evoke EMG activity in contralateral muscles. Several safety studies have suggested that single stimuli TMS can be used without risk of side effects such as epileptic seizures or transitory memory impairment in all normal subjects (Bridgers and Delaney, 1989; Dressler et al., 1990). Although TMS has been reported to induce seizures in patients with partial or generalised epilepsy (Tassinari et al., 1990; Hufnagel and Elger, 1991; Classen et al., 1995), and one patient with a recent stroke (Homberg and Netz, 1989); it has also been safely applied to diverse patient groups, including those with Parkinson's disease (Ridding et al., 1995), multiple sclerosis (Mayr et al., 1991), and epilepsy (Tassinari et al., 1990).

Although most studies have used single pulses of TMS, there has been much recent interest in the possibility of applying repeated stimuli for periods of up to several seconds. The potential advantage of giving trains of stimuli is considerable. For example, a single shock can disrupt brain activity for 100 ms or so, whereas a train of stimuli poten-

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0924-980X/97/$17.00 © 1997 Elsevier Science Ireland Ltd. All rights reserved
PII S0924-980X(97)00057-X

EEM 96713

tially can disrupt activity for the duration of the train, making it much easier to detect processing changes in behavioural studies. However, several studies have also shown that repetitive TMS can induce generalised epileptic seizures even in persons with no known history of epilepsy (Pascual-Leone et al., 1993; Wassermann et al., 1996). Two safety studies of rapid-rate TMS (rrTMS) have been conducted (Pascual-Leone et al., 1993, 1994), which have set out some of the parameters for 'safe' rrTMS. These studies have yielded useful safety guidelines for the application of long trains of stimuli. An unforseen problem, however, was noted recently by Wassermann et al. (1996). In their experiments, subjects were given several trains of shocks each separated by a short interval. Even though the parameters of each train lay within safety limits reported by Pascual-Leone et al. (1993), two subjects experienced seizures. The first seizure occurred after 15 Hz rrTMS over the left prefrontal cortex at 1.2 times motor threshold with an inter-train interval of 250 ms. The second seizure was in a 39-year-old woman after 4 consecutive 800 ms trains of 25 Hz, with inter-train intervals of 1 s, with rrTMS over the motor cortex. Wassermann et al. (1996) concluded that new guidelines for the use of brief concatentated trains must be found.

The present study was designed to address this question of safety of concatenated trains of rrTMS within a predefined range of stimulation parameters. The disruptive effect of a single shock depends on stimulus intensity, being longer for larger shocks. However, a larger shock is less focal, so that it is more difficult to localise its action to particular cortical areas. To overcome this we wanted to use short trains (4 stimuli) of smaller shocks separated by 50 ms or so. In this way we hoped to be able to reduce stimulus spread and maximise the duration of disruption. The parameters chosen were based on an experiment described by Amassian et al. (1990). A single magnetic stimulus over the occiput can suppress perception of letters if given 70–120 ms after a brief visual stimulus. Amassian et al. (1993) showed that suppression also occurred if 3 small stimuli (each of which alone was ineffective in suppressing visual perception) separated by 70 ms or so were given. Such a combination of short trains of small shocks maximises the effectiveness of stimulation whilst maintaining focality. In addition, the short duration of the train means that a range of stimulus intensities can be explored within existing safety guidelines. In the present experiment, in each of two separate blocks, 50 trains of 4 shocks were given to the motor cortex every 3.2 s at an intensity of 5–10% above active motor threshold.

2. Methods

2.1. Subjects

Six healthy normal control subjects (4 male and 2 female) volunteered to take part in the study following informed consent which was obtained according to the guidelines set out by the Ethics Committee of the National Hospital for Neurology and Neurosurgery. All subjects were staff or visiting scientific staff at the MRC Human Movement and Balance Unit. Prior to recruitment, all subjects were asked a number of screening questions relating to the exclusion criteria which were as follows:

1. Subjects with a history of a medical or neurological illness
2. Subjects who had undergone a neurosurgical procedure
3. Subjects currently taking any prescribed or unprescribed medication
4. Subjects with a personal or a family history of epilepsy, including a personal history of febrile convulsions
5. Subjects with a history of substance abuse
6. Subjects with pacemakers, cochlear implants, or surgical clips
7. Female subjects who were, or considered that they may be, pregnant

One potential subject was excluded because of a history of infantile febrile convulsions. The procedures of the study were explained to subjects, before ensuring that subjects met the selection criteria and obtaining informed consent. All subjects were made aware of the fact that the study they were being asked to participate in was to establish the 'safety' of rrTMS. In addition to specifying the stimulation parameters, the written information sheet stated that the technique carried the risk of an epileptic seizure. All subjects had previously participated in studies using single pulse TMS. All subjects were right-handed, with a mean score of 92.8 (SD = 10.6) on the Handedness Inventory (Oldfield, 1971). The mean age was 33.3 years (SD = 5.9, range = 26–42).

2.2. Parameters of rapid rate TMS (rrTMS)

For rrTMS, we used the Quadstim manufactured by the MagStim Company (Magstim, 1996). This consists of 4 separate High Power Magstim 200 units which are connected together through the same high performance stimulating coil. The power of each unit, as well as the time of discharge, can be controlled independently.

The parameters of rrTMS selected were within published safety guidelines (Pascual-Leone et al., 1993, 1994). We used a train of 4 stimuli, with an inter-stimulus interval of 50 ms, i.e. a rrTMS frequency of 20 Hz. A block involved 50 trains of rrTMS. The interval between trains was 3.2 s. This was limited by the equipment and was the minimum inter-train interval at which trains at the rate of 20 Hz could be administered at intensities above 50% of stimulator output. Two such blocks of rrTMS were given, with a minimum break of 10 min between blocks. The stimulus intensity was set to be 5–10% above each individual's active motor threshold. The active motor threshold was established

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over the left motor cortex by determining the minimum stimulator output which reliably gave rise to visible movement of the outstretched right hand and motor evoked potentials (MEPs) in the right first dorsal interosseous. Stimulation was given with the subject in a relaxed state. rrTMS was given over the left motor cortex using a 'figure of 8' coil with an internal diameter of 5 cm for each loop. The optimal coil position was determined by examining the amplitude of MEPs. In all cases this resulted in the coil being held in an anterior-posterior orientation through the optimal site. For 3 of the subjects the coil was held in an orientation that optimised current flow in the motor cortex, and for the other 3 subjects the coil was held in the reverse orientation. For the latter 3 subjects, the absolute intensity of stimulation was in fact higher, although the percentage above threshold was set to the same value. The reason for employing both optimal and non-optimal coil orientations relates to our aim to conduct a series of experiments on cognitive function in the future, where the stimulator will be applied over different frontal or parietal areas of the scalp. The optimal orientation of the coil is influenced by the relative orientation of neurones in the cortex below the coil. Since we do not know what this orientation may be in 'silent' cortical areas, we decided to explore both the most effective and the least effective methods of stimulating the motor cortex.

2.3. Procedure and assessment measures

The study was conducted by researchers experienced in the use of TMS in a room supplied with resuscitation and EEG monitoring equipment. The whole procedure was recorded on videotape. Each subject took part in the following assessments.

2.3.1. Neurological examination

The neurological examination was carried out by the same neurologist immediately before and after the two blocks of rrTMS. This included measurement of blood pressure, pulse rate, time taken to walk a standard distance of 10 m at a normal pace and at a fast pace, two point discrimination at the tip of right and left index fingers, and assessment of balance. Balance was assessed by recording the number of mis-steps and the total time taken to tandem-walk a standard distance of 5 m forwards and backwards. Measurements of blood pressure and pulse rate were also obtained in the break between the two blocks of rrTMS.

2.3.2. EEG and EMG recording

All recordings were made with Digitimer D150 amplifiers and non-polarizable Ag/AgCl electrodes. EEG was recorded from electrodes placed at F3, Fz, F4, C3, Cz, C4, T1, T2, P3, Pz, and P4. Bipolar recordings were made from electrodes in each transverse chain. The subject was grounded on the left wrist. The high frequency cut-off was set at 100 Hz, the time constant was 1 s. EEG was recorded for 10 min before and after each block of rrTMS. To avoid scalp burns (Pascual-Leone et al., 1990; Roth et al., 1992), during rrTMS, the scalp electrode overlying the left motor cortex was removed. During rrTMS, EMG was recorded bipolarly (High frequency cut-off 3 kHz, time constant 3 ms, sensitivity 1 mV) from the right first dorsal interosseous (FDI), the right abductor digiti minimi, right forearm flexors, right forearm extensors, right biceps and right deltoid muscles.

2.3.3. Assessment of cognitive function

All subjects were assessed on tests of cognitive function relating to memory, attention and executive function, before and after two blocks of rrTMS. To minimise practice effects, parallel forms of the tests were used. The tests used were: Rey Auditory Verbal Learning, Digit Span forward and backward, Paced Visual Serial Addition Test, Verbal Fluency, Reitan Trail Making Test (for details see Lezak, 1983).

2.3.4. Assessment of motor speed and manual dexterity

Measures of unwarned visual simple reaction time (SRT, see Jahanshahi et al., 1992 for details) and manual dexterity (Purdue Pegboard, see Lezak, 1983) were obtained before and after two blocks of rrTMS. On each occasion, SRT involved 40 trials performed in separate blocks with each hand. Reaction time (the time between presentation of the stimulus and subject responding by lifting index finger from 'home' key) and movement time (the time between subject lifting index finger from the 'home' key and pressing a 'response' key positioned 4 inches above it) were measured to the nearest ms. For the Purdue Pegboard subjects were required to insert pegs for 30 s using the right and the left hands and then bimanually.

2.3.5. Checklist of symptoms

Following each block of rrTMS, subjects were asked to report whether during or after cessation of rrTMS they had experienced any of the following symptoms: headache, visual disturbance, weakness, paresthesias, instability, vertigo, tinnitus, changes in hearing or any other bodily sensations.

3. Results

The average active motor threshold of the 3 subjects studied with the optimal coil orientation was 43% (range 38–48%) of the stimulator output, while it was 62% (range 60–66%) for the 3 subjects in whom a non-optimal orientation was used. For the sample as a whole, active motor thresholds ranged from 38 to 66% of the stimulator output (mean = 52.5, SD = 11.4). The intensity of rrTMS which

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Table 1

The results of the neurological examination in each of the 6 subjects before and after two blocks of rrTMS

Subject	Age (years)		Blood pressure systolic/diastolic (mmHg)	Pulse rate (beats/min)	Balance forwards	Balance backwards	Walk normal (min)	Walk fast (min)	Two point discrimination (mm)	
									right	left
1 Male	42	Pre	122/77	53	19.1	19.7	9.4	7.1	1.5	1.0
		Post	117/79	53	17.3	19.5	9.2	7.2	1.5	1.0
2 Male	26	Pre	158/95	58	17.3	14.1	8.8	6.5	2.5	2.5
		Post	160/100	64	14.4	13.7	9.5	6.9	2.0	2.0
3 Male	38	Pre	129/82	71	8.4	10.6	7.7	5.6	1.0	1.0
		Post	123/78	76	8.1	10.8	8.6	6.3	1.0	1.0
4 Male	34	Pre	155/90	70	14.8	14.5	9.9	7.2	2.0	2.0
		Post	153/93	62	18.3	16.3	9.7	7.5	2.0	2.0
5 Female	31	Pre	145/90	74	13.2	12.9	8.5	6.38	2.0	2.0
		Post	135/90	70	Miss.	12.9	8.5	6.38	2.0	2.0
6 Female	29	Pre	114/81	72	15.4	7.3	9.3	7.3	0.8	1.5
		Post	105/71	71	12.6	7.6	8.7	7.6	0.8	1.5
Mean		Pre	137.2/85.8	66.3	14.7	13.2	8.9	9.0	1.6	1.7
SD			18.2/6.9	8.6	3.7	4.2	0.75	0.52	0.65	0.61
Mean		Break	134/85.8	67.3						
SD			15.9/9.9	8.7						
Mean		Post	132.2/85.2	65.7	14.1	13.5	6.7	7.0	1.6	1.6
SD			21.3/10.9	7.9	4.1	4.1	0.64	0.58	0.54	0.49

Mean and standard deviation (SD) scores are also presented for the assessment immediately before (Pre) and immediately after (Post) two blocks of rrTMS as well as for the break between the two blocks. Miss., data missing.

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was 5–10% above threshold ranged from 48 to 73% of the stimulator output.

3.1. Measures of neurological, motor and cognitive function

The individual data and the mean scores for the various measures obtained from assessment of neurological, cognitive and motor function are presented in Tables 1, 2 and 3. The pre and post-rrTMS data were compared using a series of Wilcoxon Matched Pairs tests. The two blocks of rrTMS did not produce any significant changes in any of the measures listed in Tables 1 and 2 and Table 3. The only changes that approached significance were RTs which were slightly

Table 2

The results of the assessment of cognitive function in each of the 6 Subjects immediately before (Pre) and after (Post) two blocks of rrTMS

Subject	Digit Span score		RAVLT number recalled			PVSAT errors		Verbal fluency	Reitan	
	F	B	T1	T5	Delay	0.25	0.5Hz		s	s
1 Pre	13	10	8	15	13	0	0	17.7	40	37
Post	12	13	10	15	14	0	0	15.7	27	28
2 Pre	9	11	7	13	11	5	1	12.3	23	39
Post	13	12	6	14	14	2	4	15.0	19	38
3 Pre	6	10	9	14	Miss.	2	8	12.3	22	78
Post	4	6	7	13	10	1	3	15.0	27	47
4 Pre	10	11	8	13	11	0	3	15.3	38	45
Post	8	8	6	12	7	0	0	11.3	21	48
5 Pre	10	7	9	14	14	2	0	13.0	16	57
Post	7	8	8	15	15	0	2	17.7	14	40
6 Pre	9	8	7	15	15	1	1	23.7	19	27
Post	13	8	8	14	12	0	0	16.0	12	40
Mean Pre	9.5	9.5	8	14	12.8	1.7	2.2	16.5	26.3	47.2
SD	2.3	1.6	0.89	0.89	1.8	1.9	3.1	4.1	10.1	18.1
Mean Post	9.5	9.2	7.5	13.8	12	0.5	1.5	15.5	20	40.2
SD	3.7	2.7	1.5	1.2	3.0	0.84	1.8	2.3	6.3	7.2

Mean and standard deviation (SD) scores are also presented.
Digit Span: F, forward; B, backward; RAVLT, Rey Auditory Verbal Learning Test; T1, Trial 1; T5, Trial 5; Delay, delayed recall after 45 min; PVSAT, Paced Visual Serial Addition Test at a slow and fast rates; VF, First Letter Verbal fluency, mean of 3 trials; Reitan, Reitan Trail Making Test, time taken to complete Versions A and B in seconds. Miss., data missing.

Table 3
The results of the assessment of motor function in each of the 6 subjects immediately before (Pre) and after (Post) two blocks of rrTMS

Subject	RT		MT		Pegboard			
	R	L	R	L	Unimanual		Bimanual	
	ms	ms	ms	ms	R	L	R	L
1 Pre	281	223	93	102	20	18	14	14
Post	260	231	89	114	17	16	14	14
2 Pre	257	257	114	125	12	13	13	13
Post	245	227	91	97	14	13	13	13
3 Pre	241	242	60	84	18	21	16	16
Post	231	230	65	50	20	16	17	17
4 Pre	255	263	112	117	15	14	12	12
Post	251	262	109	120	16	15	13	13
5 Pre	295	300	163	157	19	12	13	13
Post	269	291	146	156	14	14	12	12
6 Pre	245	252	121	110	19	16	14	15
Post	255	254	138	153	20	19	16	16
Mean Pre	262.3	256.2	110.5	115.8	17.2	15.7	13.7	13.8
SD	21.2	25.6	33.9	24.6	3.1	3.4	1.4	1.5
Mean Post	251.8	249.2	106.3	115.0	16.8	15.5	14.2	14.2
SD	13.1	25.0	31.1	39.2	2.7	2.1	1.9	1.9

Mean and standard deviation (SD) scores are also presented.
RT, Reaction time with right (R) and left (L) hands; MT, movement time with right (R) and left (L) hands; Peg, number of pegs inserted with right and left hands under unimanual and bimanual conditions.

faster (mean change of 10.5 ms with the right hand and 7 ms with the left hand, $P = 0.09$) and systolic blood pressure which was lower (mean change of 5 mm Hg, $P = 0.059$) after two blocks of rrTMS.

rrTMS at the selected parameters did not produce any major adverse effects on any of the subjects. Two subjects reported paraesthesia in the fingers of the right hand during rrTMS which ceased at the end of the stimulation. The two subjects who were stimulated at the highest intensities (70 and 73% of stimulator output) reported slight pain at the site of stimulation during rrTMS.

3.2. EEG and EMG recording

The EEG was inspected by one of us (MR) with considerable experience in recording clinical EEG. The EEG record of all 6 subjects was considered to be normal both before and after two blocks of rrTMS, as well as in the break between the two blocks of stimulation.

For 4 of the subjects, the EMG record showed no evidence of summation or spread of activity across the 50 trials in a block or across blocks. This is illustrated by the EMG records of Subject 6 shown in Fig. 1, which shows the size of the MEPs remained relatively constant from Trial 2 to 25 to 50 in the first as well as in the second block of rrTMS. In contrast, for two of the subjects, there was some evidence of magnification of activation across the 50 trials. For Subject 3, a 38-year-old male, stimulated at 52% of stimulator output, there was a gradual increase in the size of the MEP recorded from the biceps and deltoid muscle in the course of the 50 trials in the first block (Fig. 2). Biceps responses increased from an average (over 5 consecutive trains) peak-to-peak size of 1–4 mV, whilst deltoid increased from 50 to 150 μV. This was also visually evident on the videotape as lifting movements of the forearm of gradually increasing size. There was no evidence of spread of activity to other muscles. For example, the mean amplitude for FDI at the start and end of the block was 1.25 and 1.5 mV, respectively. This gradual increase in responses in the biceps did not occur in the second block of rrTMS (Fig. 2). A similar effect which occurred only in the second block of trials was also observed for Subject 2, a 26-year-old male stimulated at the highest intensity, 73% of stimulator output. Thus, even in these two subjects there was no evidence for spread of activation nor of after-discharges in the EMG.

4. Discussion

The novel feature of the present study was that we assessed the safety of rrTMS when using a relatively large number (50) of short trains of small stimuli (4 shocks with inter-stimulus-interval of 50 ms) separated by inter-train intervals of 3.2 s. The results showed that two blocks of rrTMS using these parameters produced no major adverse effects on any of the subjects. There was no significant change in measures of neurological and cognitive function, reaction time and movement times or manual dexterity, and the EEG was unchanged. These results are in general agreement with those of previous safety studies of single pulse TMS or rrTMS (Bridgers and Delaney, 1989; Pascual-Leone et al., 1993).

Two subjects experienced short-lasting parathesia during stimulation. Pain at the site of stimulation was reported by

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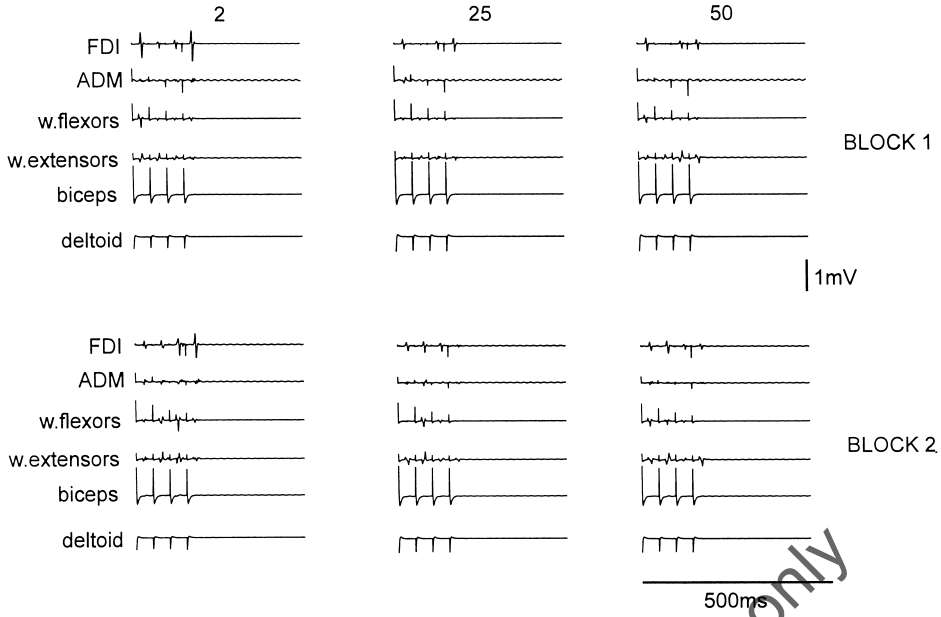

Fig. 1. EMG recorded during the first (top row of data) and second (bottom row of data) blocks of rrTMS from Subject 6. The records show EMG recorded from first dorsal interosseus (FDI), abductor digit minimi (ADM), wrist flexors (w. flexor) extensors (w. extensors), biceps, deltoid. The train of 4 magnetic stimuli starts at the beginning of the records and produces 4 sharp artefacts that can be distinguished in all traces. In some muscles, these artefacts are followed by EMG responses 15–20 ms later. (The stimulus artefacts are perhaps clearest in the deltoid traces, where short-latency EMG responses are small or absent.) Each set of 6 records is from a single stimulus train. The 3 sets on the top row show the responses recorded on the 2nd, 25th, 50th train of the first block of trials. Comparison of records across these trials shows that no change in the size of the MEPs occurred for any of the muscles within or across the two blocks of rrTMs.

the subjects stimulated at the highest intensities. In one 38-year-old male subject, muscle activity in the arm muscle contralateral to the site of activation became gradually larger in size across the 50 trials of rrTMS. A similar increase in effectiveness was also observed in the second block in a 26-year-old male subject, who was stimulated at the highest intensity (73% stimulator output). The mechanisms for this increase of excitability are not clear. Failure of intracortical

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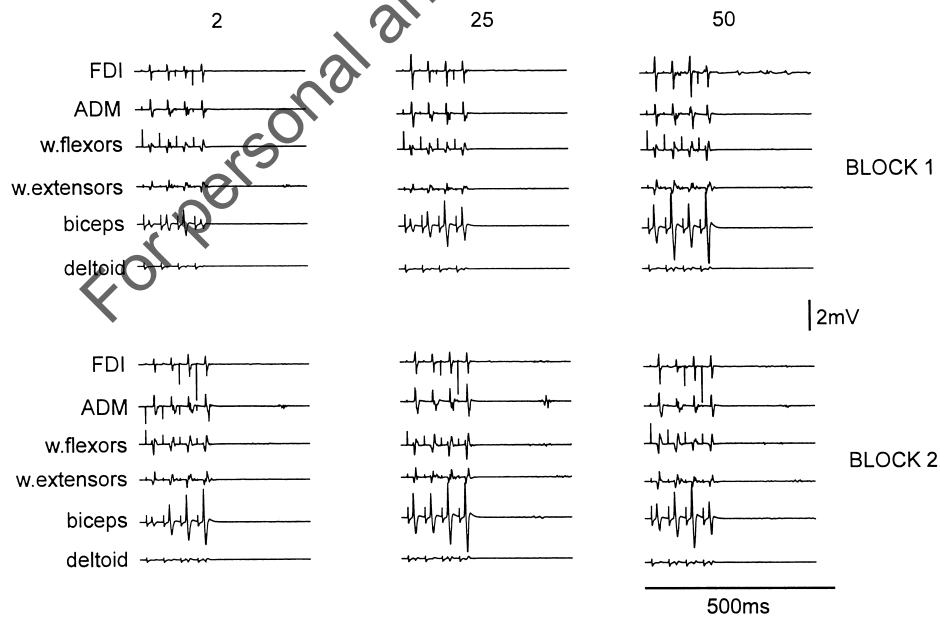

Fig. 2. EMG recorded during the first (top row of data) and second (bottom row) blocks of rrTMS from Subject 3. The records show EMG recorded from first dorsal interosseus (FDI), abductor digiti minimi (ADM), wrist flexors, extensors (w. flexor, w. extensors) biceps, deltoid. The train of 4 magnetic stimuli starts at the beginning of the records and produces 4 sharp artefacts that can be distinguished in all traces. In some muscles, these artefacts are followed by EMG responses 15–20 ms later. (The stimulus artefacts are perhaps clearest in the deltoid traces, where short-latency EMG responses are small or absent.) Each set of 6 records is from a single stimulus train. The 3 sets on the top row show the responses recorded on the 2nd, 25th, 50th train of the first block of trials. Comparison of records across these trials shows a small increase in the size of the MEPs recorded from the biceps and deltoid in the first rrTMS block which did not occur in the second block.

inhibition has been proposed as one likely mechanism (Pascual-Leone et al., 1994).

Our results generally confirm the safety of repeated trains of rrTMS at relatively high frequencies (20 Hz) and relatively low intensities (10% above active motor threshold). We have in fact gone on to safely apply rrTMS using similar parameters in a study of an attention-demanding cognitive task, random number generation (Jahanshahi et al., 1997). Eleven subjects received 3 blocks of rrTMS over the prefrontal cortex on two separate days. Each block involved 50 trains of 4 shocks with an intershock interval of 50 ms and inter-train interval of 2.4 s, given at intensities equivalent to or slightly below active motor threshold. Although no adverse effects were experienced by any of the subjects, with the parameters employed, rrTMS over the left dorsolateral prefrontal cortex disrupted random number generation and altered the nature of the subject's counting bias. The disruptive effect of rrTMS over the left dorsolateral prefrontal cortex on random number generation was much greater than that obtained using single shock TMS.

The guidelines tested here pertain to limited numbers of shocks. Recently, new stimulators have become available that allow administration of prolonged trains of stimuli. There has been interest in rrTMs over more prolonged periods as a treatment for depression (George et al., 1995). Concerns have been raised regarding the remote possibility of delayed malignancy with such prolonged exposure to low frequency electromagnetic fields (Brown, 1996). Other studies will be necessary to address this question. The present investigation demonstrates the short-term safety of limited blocks of rrTMS.

The particular rrTMS parameters were selected to approximate requirements for studies of cognitive function. For example, if a hypothetical cognitive task takes 1 s to perform, disruption of processing for 10 ms, is only 1% of the total time taken and hence is unlikely to lead to significant effects on performance. Disruption for 100–200 ms or 10–20% of processing time is much more likely to produce a measurable effect on performance. In order to achieve this duration with just a single stimulus a large intensity is required. This is both uncomfortable for the subject and has the disadvantage that the effect will spread over a considerable area of cortex and spatial localisation will be lost. Another solution is to use a train of small stimuli such that the disruptive effect is prolonged whilst maintaining a relatively good spatial accuracy. The present study has shown that repeated short trains of rrTMS are safe when using parameters falling within published safety guidelines (Pascual-Leone et al., 1993). As originally demonstrated by Amassian et al. (1990) for visual perception, Grafman et al. (1994) and Pascual-Leone et al. (1996) when respectively studying explicit memory and implicit learning, and confirmed in our study on random number generation (Jahanshahi et al., 1997), rrTMS has the potential of becoming a useful tool for cognitive neuroscientists as it provides the possibility of inhibition/activation of specific cortical regions at specific time points during the performance of cognitive tasks. The temporal and relative structural specificity of rrTMS can help define whether specific parts of the cortex are involved in a particular cognitive task and at what time their function is essential.

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Acknowledgements

The financial support of the Wellcome Trust and the Medical Research Council (UK) is gratefully acknowledged.

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