

Stimulation over the human supplementary motor area interferes with the organization of future elements in complex motor sequences

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Summary

We used high-frequency repetitive transcranial magnetic stimulation (rTMS) to study the role of the mesial frontocentral cortex (including the supplementary motor area) in the organization of sequential finger movements of different complexity in humans. In 15 subjects, rTMS was randomly applied to the scalp overlying the region of the supplementary motor area and over other positions, including the contralateral primary motor cortex (hand area) during the performance of three overlearned finger sequences on an electronic piano. In all trials, rTMS (frequency 15–20 Hz) started 2 s after the first key press and lasted for ~2 s. All sequences were metronome-paced at 2 Hz and retrieved from memory. The ‘simple’ sequence consisted of 16 repeated index finger key presses, the ‘scale’ sequence of four times four sequential key presses of the little, ring, middle and index fingers, and the ‘complex’ sequence of a much less systematic and, therefore, more difficult series of 16 key

presses. To measure the effects of rTMS interference with regional cortical function, we analysed rTMS-induced accuracy errors in the movement sequences. Stimulation over the supplementary motor area induced accuracy errors only in the complex sequence, while stimulation over the primary motor cortex induced errors in both the complex and scale sequences, and stimulation over other positions (e.g. F3, F4, FCz, P3, P4) did not interfere with sequence performance at all. Stimulation over the supplementary motor area interfered with the organization of subsequent elements in the complex sequence of movements, with error induction occurring ~1 s later than with stimulation over the primary motor cortex. Our findings are in keeping with recent results in non-human primates (Tanji J, Shima K. *Nature*, 1994; 371: 413–6) indicating a critical role of the supplementary motor area in the organization of forthcoming movements in complex motor sequences that are rehearsed from memory and fit into a precise timing plan.

Keywords: supplementary motor area; finger movements; motor sequences; motor control

Abbreviations: ANOVA = analysis of variance; c-M1 = contralateral primary motor cortex; fMRI = functional MRI; iM1 = ipsilateral primary motor cortex; MEP = motor evoked potential; rTMS = repetitive TMS; TMS = transcranial magnetic stimulation

Introduction

The role of the human mesial frontocentral cortex, including the supplementary motor area, in motor information processing remains enigmatic. In addition to the supplementary motor area ‘proper’ other regions of the mesial frontal cortex, such as pre-supplementary motor area (Tanji and Shima, 1996) and various cingulate motor areas (Picard and Strick, 1996), are also likely to be active in motor control. There is particular interest in understanding the functions of these mesial structures, especially of the supplementary motor area,

since diseases such as Parkinson’s disease have been linked to dysfunction of the supplementary motor area (Dick *et al.*, 1989; Jenkins *et al.*, 1992; Playford *et al.*, 1992; Rascol *et al.*, 1992, 1993, 1994; Cunnington *et al.*, 1995, 1996; Jahanshahi *et al.*, 1995).

In humans, the function of the mesial frontocentral motor areas has been quite difficult to assess, in part because the supplementary motor area and cingulate gyrus are largely buried in the median fissure, which may cause distortion and

partial cancellation of electrical signals generated in these areas. Nevertheless, many EEG and magnetoencephalographic studies in normal subjects and patients with supplementary motor area lesions have suggested that the supplementary motor area participates significantly in movement preparation and execution (Kornhuber and Deecke, 1965; Deecke and Kornhuber, 1978; Deecke *et al.*, 1987; Barrett *et al.*, 1986; Lang *et al.*, 1990, 1991; Ikeda *et al.*, 1992, 1993, 1995; Toro *et al.*, 1993; Rektor *et al.*, 1994). More recently, neuroimaging studies using PET or functional MRI (fMRI) have shown activation of the human supplementary motor area and cingulate cortex associated with the performance of repetitive and sequential movements (Roland *et al.*, 1980; Colebatch *et al.*, 1991; Grafton *et al.*, 1992; Rao *et al.*, 1993; Shibasaki *et al.*, 1993; Deiber *et al.*, 1996; Hikosaka *et al.*, 1996). PET and fMRI have high spatial resolution but very limited temporal resolution. Therefore, they can neither provide detailed information on the timing of task-related activation during a specific motor act, nor show the relative relevance of each cortical area for task performance. Some of this information can be obtained by means of lesion studies (Laplaine *et al.*, 1977; Brinkman, 1984; Deecke *et al.*, 1987; Lang *et al.*, 1991; Halsband *et al.*, 1993; Tanji, 1994) or, theoretically, by invasive techniques of temporary, reversible local inactivation (e.g. the sodium amobarbital test). A problem with lesion studies in humans (e.g. after ischaemic stroke) is that any structural damage might induce permanent plastic changes of individual functional brain topography (Frackowiak *et al.*, 1991; Weiller *et al.*, 1992, 1993; Wassermann *et al.*, 1996). As a consequence of this reorganization, different neural structures may be involved in the processing of certain motor tasks in a patient's brain compared with those involved in the intact brain.

Transcranial magnetic stimulation (TMS) is a noninvasive means of interfering with local cortical function (Cohen *et al.*, 1991; Pascual-Leone *et al.*, 1991, 1994a; Amassian *et al.*, 1993a, b, 1994; Grafman *et al.*, 1994; Muri *et al.*, 1994, 1995; Chen *et al.*, 1997). A few attempts have been made to stimulate the supplementary motor area noninvasively with single magnetic pulses, but the results were contradictory with respect to the performance of finger-movement sequences in normal subjects (Amassian *et al.*, 1990; Cunnington *et al.*, 1996). In contrast to single-pulse TMS, high-frequency repetitive TMS (rTMS) makes use of temporal summation of the effects of a train of stimuli, and it can disturb the function of a cortical area effectively for the duration of the stimulus train. Accordingly, we applied rTMS over the region of the supplementary motor area to study its role in the organization of overlearned unimanual finger-movement sequences in humans. We tested two hypotheses. (i) If supplementary motor area involvement is increasingly critical for task performance with increasing movement complexity as suggested by PET data (Shibasaki *et al.*, 1993), then transient dysfunction of this structure should interfere more with complex than with simple movement

sequences. (ii) If the human supplementary motor area is particularly involved in the planning of forthcoming movements in a motor sequence retrieved from memory, as has been demonstrated in monkeys (Halsband *et al.*, 1994; Tanji and Shima, 1994, 1996), then its induced dysfunction should interfere with the composition of future elements in a movement sequence.

Methods

The study consisted of three main experiments (Experiments 1–3) and two control experiments (Control experiment 1 and 2). In Experiment 1, the effects of rTMS applied to the frontocentral midline on the performance of three finger sequences of different complexity were studied (12 subjects). In Experiment 2, the effects of rTMS over the frontocentral midline were compared with effects of rTMS over other scalp positions (12 subjects). In Experiment 3, the timing patterns of error induction were compared between rTMS applied to the frontocentral midline and to the primary motor cortex (M1) (13 subjects). Control experiment 1 studied the correlation of rTMS-induced EMG activity with rTMS effects on task performance (six subjects). Control experiment 2 addressed the question whether subjects could compensate for the rTMS-induced interference if a large number of rTMS trains was given repeatedly (five subjects). We have previously shown that effects comparable to rTMS-induced interference cannot be elicited by either peripheral magnetic stimulation of forearm muscles or deprivation of visual, acoustic or tactile sensory feedback during sequence performance (Chen *et al.*, 1997).

Subjects

We studied 15 healthy subjects (six men, nine women), aged 21–64 years (median 40 years). According to the Edinburgh inventory (Oldfield, 1971), 13 subjects were right-handed, and two were ambidextrous. The subjects were naive to the experimental purpose of the study and did not regularly play the piano. The protocol was approved by the National Institutes of Health Review Board, and the subjects gave their written informed consent for the study.

Experiments 1–3

Finger sequences

Subjects played three finger sequences of different complexities with the right hand following a metronome beat at 2 Hz. The fingers were numbered as follows: little finger, 5; ring finger, 4; middle finger, 3; index finger, 2 (*see* Fig. 1). Common elements in all sequences included rate (2 Hz), mode of external pacing (metronome, acoustic), and total number of key presses ($n = 16$, resulting in a sequence duration of ~8 s). In each experiment, the three finger

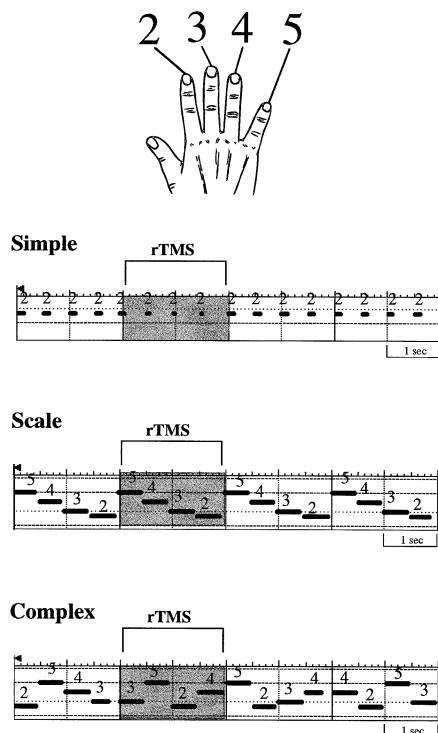


Fig. 1 Finger sequences used. Shaded areas indicate periods of repetitive transcranial magnetic stimulation (rTMS). The numbers correspond to the individual fingers as depicted in the diagram. The heavy black lines indicate the key presses. Their vertical positions indicate which key was pressed on the piano. Time interval between two vertical lines is 1 s. Total sequence length = 8 s (= 16 key presses at 2 Hz).

sequences (simple, scale and complex) were played in random order.

To perform the 'simple' sequence subjects repetitively pressed one key using the index finger (2-2-2-2-2-2-2-2-2-2-2-2-2-2-2-2) (Fig. 1). For the 'scale', they played four consecutive notes in a scale-like manner using four fingers (5-4-3-2-5-4-3-2-5-4-3-2-5-4-3-2) (Fig. 1). The scale sequence was considered more difficult than the simple sequence because four fingers were used consecutively rather than one finger repetitively. To play the 'complex' sequence, subjects used four fingers in a nonconsecutive, nonrepetitive order (2-5-4-3-3-5-2-4-5-2-3-4-4-2-5-3) (Fig. 1). In both the scale sequence and the complex sequence, each finger was used the same number of times. The average time needed to learn each sequence in a group of 12 normal subjects was significantly different between the simple sequence (37 ± 45 s) (mean \pm SD), the scale (107 ± 85 s) and the complex sequence (1193 ± 1024 s) ($P < 0.05$; Wilcoxon matched-pairs test), indicating that the sequences clearly differed with respect to their complexity, as described by the acquisition time.

Before the experimental sessions with rTMS, subjects practised the sequences until they could perform them from memory 10 times in a row, without errors. At this level of performance, the sequences were considered 'overlearned',

thus assuring constant baseline performance during the experimental sessions. It is known that in similar settings the metronome is used only as a pacemaker, i.e. the rhythmic sequential movements are not carried out as true 'reactions' to each metronome beat. On the contrary, the tones are anticipated and the metronome is used simply as a guide to maintain a regular rhythm (here, 2 Hz). This phenomenon has been termed 'negative asynchrony' (Aschersleben and Prinz, 1995).

Data acquisition

Sequences were played on an electronic piano (Yamaha pf85), which was connected to a laboratory Macintosh computer via a MIDI interface (MIDI translator, Opcode Systems, Inc., Palo Alto, Calif., USA). Special software (Vision 1.4, Opcode Systems) was used to record the key presses for further analysis. The EMG was recorded from surface electrodes placed over the bellies of the flexor digitorum superficialis and extensor digitorum communis muscles of the forearm. The EMG was sampled at 5 kHz, the high pass filter was set at 5 Hz, and the low pass filter at 1.5 kHz (DANTEC Counterpoint electromyograph, DANTEC Medical A/S, Skovlunde, Denmark).

Experimental set-up

The subject was seated comfortably in front of the piano with the forearm held in a molded wrist and forearm splint. The splint was fixed on a small board in front of the piano. This arrangement minimized wrist movements and assured independent finger movements for performance of key presses. After being informed of which sequence to play, the subject initiated each experimental run by the first key press. The subjects were instructed to complete playing each sequence in spite of interference by rTMS, even if they felt they had made mistakes. They were told not to replay parts of the sequence where they felt that mistakes may have occurred, but instead to try to continue with the original order and time-course of the sequence, as recalled (as if no error had occurred).

During each experimental session, one investigator applied the rTMS and observed the subject's motor behaviour, another investigator controlled the acquisition of the piano data, and a third investigator controlled and adjusted the stimulation parameters and monitored and recorded the EMG.

Repetitive TMS

A repetitive magnetic stimulator (Cadwell Laboratories, Kennewick, Wash., USA), with a water-cooled figure-of-eight shaped coil, was used for rTMS. This device was used for experimental purposes under an Investigational Device Exemption from the Food and Drug Administration. Each loop of the coil measures 7 cm in diameter. The two loops were essentially circular, but with a straight portion ~4 cm

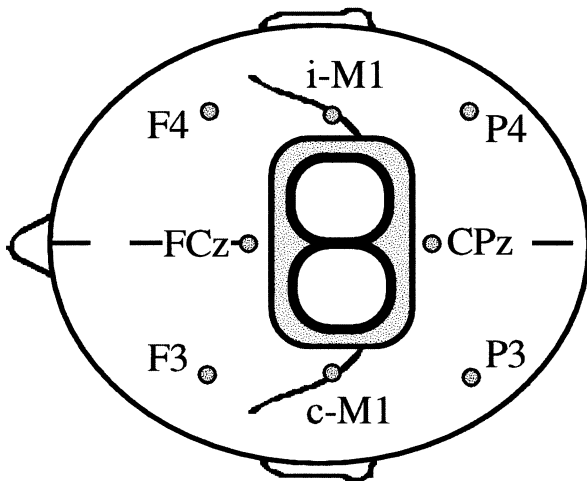


Fig. 2 Schematic diagram of the figure-of-eight shaped magnetic coil positioned on the scalp for stimulation over the supplementary motor area. Other scalp positions stimulated were located according to the international 10/20 system of electrode placement as shown in the diagram. Left is anterior and right is posterior.

long at the intersection. The coil was held tangential to the scalp, with the intersection of both loops of the coil oriented sagittally for the positions FCz, Cz and CPz (according to the international 10/20 system of electrode placement) (Fig. 2). This means that with the coil centred over Cz, an area 2 cm anterior and posterior was also covered by the coil intersection. For contralateral primary motor cortex (c-M1), ipsilateral primary motor cortex (i-M1) and the remaining positions F3, F4, P3, P4, the intersection of both loops of the coil was placed perpendicular to the expected orientation of the central sulcus. The c-M1 coil position was optimal for inducing a mild twitch in the first dorsal interosseous muscle of the performing (right) hand at rest. The i-M1 coil position was optimal for inducing a mild twitch in the first dorsal interosseous of the nonperforming (left) hand, also at rest. Accurate triggering of the stimulus was achieved with a Grass S48 pulse generator (Grass Instruments, Quincy, Mass., USA). With the first key press, a pressure transducer device was activated and sent a TTL (transistor-transistor logic) pulse to the pulse generator, which was set to generate rTMS trains after an initial delay of 2 s. Intervals between key presses without rTMS interference were very regular (e.g. mean \pm SD of 491 ± 3 ms in seven subjects). Therefore, stimulation consistently started after the fourth of the 16 key presses, usually with the onset of the fifth key press. In a few exceptional cases, subjects tended to play slightly faster than the metronome pace, which then allowed for five complete key presses before rTMS.

Determination, quantification and safety of stimulus strength. The effective strength of an rTMS train is a function of the stimulus rate, train duration and stimulus intensity. The actual stimulus intensity (stimulator output) was referenced to each subject's hand motor-threshold (for

positions over the hemispheric convexity) or leg-response threshold (for midline positions) and expressed as a percentage of that threshold.

In determining the parameters of stimulation, three general points were considered. (i) Stimulation of mesial cortical motor areas, located deeper inside the skull than those located on the hemispheric convexities, should require higher stimulus strengths than those used for disturbance of more superficial lateral motor areas. Therefore, for stimulation over midline positions, the stimulus intensity was related to the leg-response threshold rather than to the hand motor-threshold. (ii) Individual subjects show different tolerance for each specific parameter of stimulation. For example, some subjects feel uncomfortable with rTMS at higher rates, but tolerate higher stimulus intensities well. In other subjects, the situation is just the opposite. Therefore, we customized the stimulation parameters to each individual's subjective perception of comfort or discomfort. Once the parameters were set for each subject, they were kept constant throughout the experiment. (iii) All stimulation parameters were within the boundaries of safety as previously defined (Pascual-Leone *et al.*, 1993). No adverse reactions occurred during the study.

The procedure of detecting a behaviourally effective stimulation strength was as follows: While the subject played the most difficult sequence (complex), the stimulus intensity was increased stepwise until accuracy errors occurred unequivocally in at least three repeated trials. This was done separately for the supplementary motor area and c-M1 positions. Once the individual rTMS parameters were set, the order of playing the three different sequences (Experiments 1 and 2) and the different stimulation positions (Experiments 1–3) were randomized to avoid order effects.

Stimulation parameters: hemispheric convexities (c-M1, i-M1, F3, F4, P3 and P4). The hand motor-threshold was defined as the minimal output of the stimulator capable of inducing five slight twitches of the index finger (i.e. of the first dorsal interosseous muscle) in 10 single stimuli applied to the optimal scalp position for eliciting finger movements. For the 15 subjects studied, the motor threshold for the first dorsal interosseous was $64 \pm 8\%$ of stimulator output. The stimulation parameters required to elicit behavioural effects over the c-M1 were: stimulus rate, 15 Hz (except for one subject who needed 20 Hz); train duration, 1.9 ± 0.5 s; stimulus intensity, $103 \pm 7\%$ of first dorsal interosseous motor threshold. Data are given as mean \pm 1 SD.

Stimulation parameters: midline positions (FCz, Cz and CPz). The parameters for stimulation over midline positions were determined with reference to leg-response threshold because the leg representation in the primary motor cortex is located directly adjacent and posterior to the supplementary motor area. Therefore, stimulation strengths that are sufficient to elicit leg responses are also likely to stimulate supplementary motor area neurons. Leg-response

threshold was defined as a mild twitch in one or both legs. If no clear leg response could be elicited with a single TMS pulse (six subjects), the midline positions were stimulated at maximum (100%) stimulator output. Stimulus rate was 20–25 Hz (except for two subjects who felt uncomfortable with stimulation at these rates and in whom we reduced the rate to 15 Hz), train duration 1.8 ± 0.5 s, stimulus intensity $100 \pm 0.4\%$ of leg-response threshold which corresponded to $96 \pm 8\%$ of the stimulator output. Trains of rTMS stimuli with intensities close to, or even below, the single-pulse motor threshold of a cortical target area are capable of interfering with motor performance. For example, with primary motor cortex stimulation the minimum intensity necessary to induce key-press errors in the complex sequence was $96 \pm 6\%$ of the first dorsal interosseous motor threshold (Corwell *et al.*, 1996). This indicates that due to temporal summation of the stimulus effects in a train of rTMS pulses, stimulus intensities below 100% of the (single-pulse) motor threshold can be effective. This is the reason why, in the present study, it was possible to interfere with the function of the supplementary motor area even in the six subjects whose leg response-thresholds were greater than maximum stimulator output when a single pulse was applied. Intervals between trains were ≥ 1 min. Data are given as mean ± 1 SD.

Piano data analysis

To quantify the effects of rTMS on sequence performance, we analysed accuracy errors (erroneous key presses on the piano keyboard). For exact determination of accuracy errors, each recorded sequence was compared with a correct sequence template, and all key presses not matching the template were counted as errors (Experiments 1 and 2). In addition, all sequence recordings were inspected visually to describe the nature of the accuracy errors in more detail. To determine the timing of error induction with stimulation over the supplementary motor area compared with stimulation over the c-M1 (Experiment 3), the first and last wrong key press in each sequence played was visually detected and numbered with respect to rTMS onset (e.g. accuracy errors beginning with the first or second keypress after rTMS onset). Due to the regularity of the inter-key press-intervals (*see* Repetitive TMS), it was possible to convert 'number of key presses' into 'time of key press after rTMS onset' in seconds (number of key presses after rTMS onset/2). This was done to describe the timing of error induction relative to the duration of the rTMS train.

Statistical analysis

Analysis of variance (ANOVA) and the *post hoc* Scheffe test were used to compare the effects of rTMS at each scalp position on different sequences (main effect for sequence; Experiment 1) and to compare the effects of stimulation over different scalp positions on each sequence (main effect for position; Experiment 2). The nonparametric Mann–Whitney

U test was used to compare the onset and end-point of the rTMS-induced disturbance in the scale and complex sequences (Experiment 3). Effects were considered significant if $P < 0.05$.

Control experiments

The same group of subjects participated in two control experiments. The experimental setup, data acquisition and data analysis were the same as in Experiments 1–3.

Control experiment 1 ('EMG')

This experiment was designed to address the question whether stimulation over the supplementary motor area results in direct or indirect (e.g. through primary motor cortex) activation of hand muscles. The muscle activation produced by rTMS and its impact on finger sequence performance were determined by recording the EMG from the right extensor digitorum communis and tibialis anterior muscles in six subjects. We recorded the EMG from the extensor digitorum communis to determine whether the effects induced by stimulation over the supplementary motor area were due to indirect suprathreshold stimulation of the hand representation in the c-M1, either via corticocortical pathways or via spread of the magnetic field at high stimulus intensities. Stimulation-induced EMG activity was quantified by counting the number of motor evoked potentials (MEPs) elicited by rTMS. These numbers were plotted against the number of accuracy errors for three positions, Cz (overlying the supplementary motor area), c-M1 (contralateral primary motor cortex) and P3 (left parietal cortex). The EMG from the tibialis anterior was recorded to monitor muscle activity in the leg during rTMS. The nonparametric Wilcoxon matched pairs test was used to compare the number of MEPs and accuracy errors induced by stimulation over the supplementary motor area and c-M1. Effects were considered significant if $P < 0.05$.

Control experiment 2 ('Habituation')

This experiment was designed to evaluate whether there is any habituation or exacerbation of the behavioural effects when rTMS over the supplementary motor area and c-M1 is applied repeatedly at relatively short inter-train intervals within the same session. To assess this, five volunteers played the complex sequence nine times in a row, always with the same type of rTMS interference. The interval between trials was ~ 1 min. For each subject, stimulation was over either the supplementary motor area or c-M1, i.e. in the same position for all nine trials. A simple regression analysis was used to test whether there was a significant decrease or increase of errors with repeated stimuli. Effects were considered significant if $P < 0.05$.

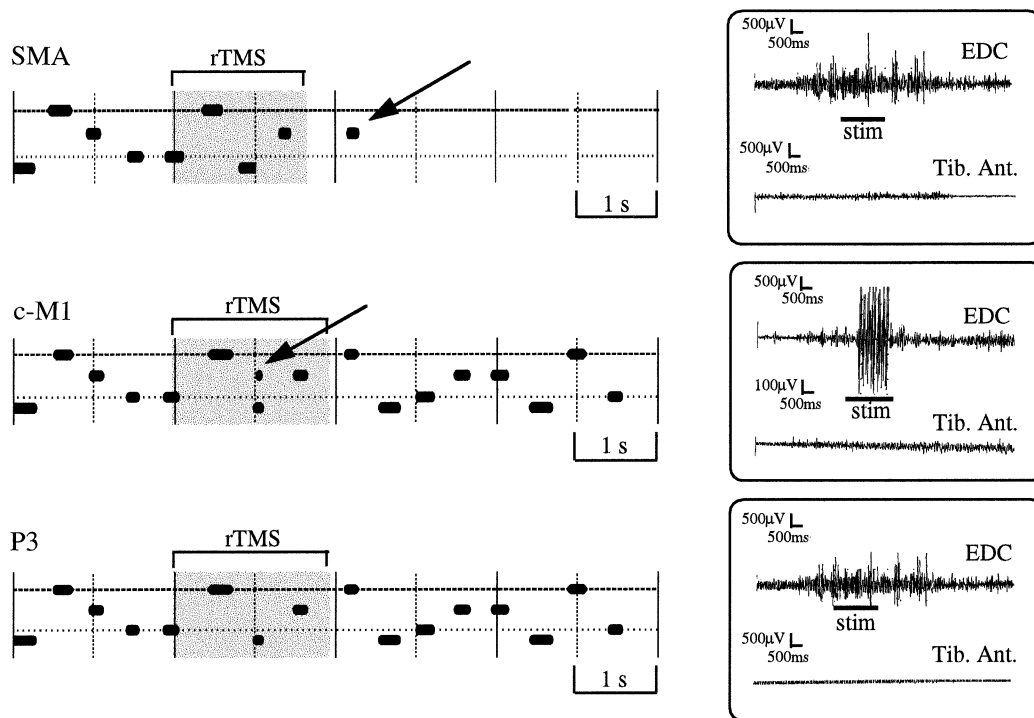


Fig. 3 Accuracy errors (arrows) and EMG findings during performance of the complex sequence with rTMS (shaded area) over three different scalp positions. *Left*: key press sequences. *Right*: corresponding EMG patterns. All traces are from the same subject. *Top left*: stimulation over the supplementary motor area (SMA). An example of delayed disturbance of the complex sequence with error onset after the end of rTMS. *Top right*: EMG activity in the extensor digitorum communis (EDC) associated with the voluntary movements (key presses). No MEPs occurred in the extensor digitorum communis or tibialis anterior (Tib. Ant.) muscles during rTMS. *Middle left*: stimulation over the c-M1. Note error onset during rTMS and the ability to continue the sequence immediately after the end of stimulation without sequence disorganization. *Middle right*: large number of MEPs in the extensor digitorum communis muscle during rTMS indicating suprathreshold c-M1 stimulation. No MEPs occurred in the tibialis anterior muscle. *Bottom left*: stimulation over P3, a control position. No accuracy errors were elicited by rTMS. *Bottom right*: EMG activity in the extensor digitorum communis muscle associated with the voluntary movements. No MEPs occurred in the extensor digitorum communis or tibialis anterior muscles during the rTMS. The EMG pattern during rTMS over P3 is essentially the same as that with rTMS over the supplementary motor area.

Results

Experiment 1: finger sequences of different complexity

Stimulation over the supplementary motor area and c-M1 resulted in significantly different effects on the three different sequences (ANOVA, main effect for sequence, $P < 0.0001$). The highest numbers of errors occurred with the most complex sequence. The complex sequence was significantly disturbed with stimulation over both the supplementary motor area (6.6 ± 4.4 errors per subject and sequence) and c-M1 (7.1 ± 3.3 errors). The less difficult scale sequence was disturbed only with stimulation over c-M1 (4.1 ± 3.6 errors). The number of errors induced during performance of the simple sequence was not significant.

The predominant types of errors evoked by stimulation over the supplementary motor area were repetition of a key press instead of pressing the next required key in the sequence and pressing entirely wrong keys (i.e. in both cases pressing extra keys = 'positive' errors), or omission of key presses

in the sequence, which often led to a complete interruption of the sequence (i.e. pressing fewer keys than required = 'negative' errors). With stimulation over the c-M1, the types of errors were similar. Negative and positive errors were similarly frequent for stimulation over the supplementary motor area (~40% negative errors, 60% positive errors) and c-M1 (~60% negative errors, 40% positive errors).

Figure 3 shows an example of how the complex sequence was disturbed by stimulation over the supplementary motor area and c-M1, but not by stimulation over a parietal position (e.g. P3). Since the scale sequence was not affected by stimulation over the supplementary motor area, no examples are presented.

Experiment 2: topography

The main effect for scalp position was significant for the complex sequence (ANOVA, $P < 0.0001$) and scale sequence (ANOVA, $P = 0.0003$). Since the number of errors induced

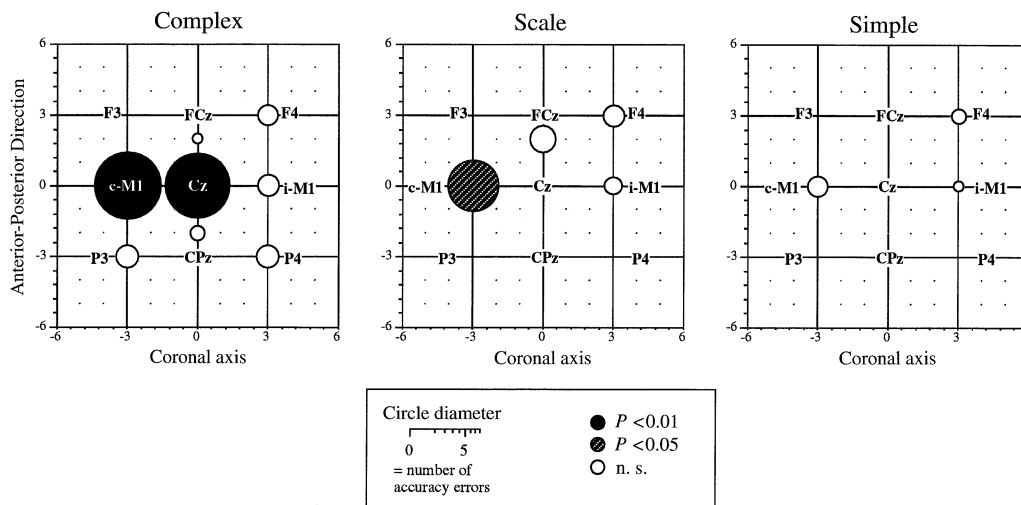


Fig. 4 Topography of disturbance effects. The number of accuracy errors (group average, $n = 12$ subjects) for each scalp position is coded by the diameter of the shaded circles (logarithmic scale). Stimulation over the supplementary motor area (position Cz) resulted in significant error induction only during performance of the complex sequence. With c-M1 stimulation, a significantly higher number of accuracy errors occurred than with stimulation of other scalp positions in both scale and complex sequences (ANOVA, *post hoc* Scheffe test). The number of errors induced with stimulation of either scalp position during performance of the simple sequence was not significant.

in the simple sequence was not significant, the topography effect was not tested for this sequence.

Stimulation over the supplementary motor area caused significantly more errors than stimulation over all other positions (ANOVA, Scheffe, $P < 0.01$), except for c-M1 (ANOVA, Scheffe, $P > 0.99$) (complex sequence only). Stimulation over the c-M1 produced significantly more errors than stimulation over the other positions (except for the position over the supplementary motor area) in both the complex sequence (ANOVA, Scheffe, $P < 0.01$) and the scale sequence (ANOVA, Scheffe, $P < 0.05$). No errors were induced by stimulation over the frontal positions F3, FCz and F4, which were the most uncomfortable and, therefore, potentially the most distracting ones to be stimulated because of rTMS-induced contractions of the frontotemporal scalp muscles. The absence of errors in these positions indicates that the effects of stimulation over the c-M1 and the supplementary motor area were not related to non-specific rTMS effects such as discomfort, startle or global attentional influences.

Figure 4 summarizes the topographic distribution of errors induced by rTMS.

Experiment 3: timing of error induction

The onset of error induction occurred significantly later with stimulation over the supplementary motor area than with stimulation over the c-M1 (for the supplementary motor area, 1.8 ± 0.8 s after rTMS onset; for c-M1, 0.7 ± 0.3 s; Mann-Whitney U test, $P < 0.01$) (Fig. 5). Additionally, the period of error induction ended later with stimulation over the supplementary motor area than with stimulation over the c-M1. With stimulation over the supplementary motor area,

error induction lasted, on average, until keypress number 11.4 ± 1.6 (corresponding to $\sim 5.2 \pm 0.8$ s) after rTMS onset; with stimulation over the c-M1 it lasted only until keypress number 4.2 ± 3.0 (corresponding to $\sim 1.6 \pm 1.5$ s) after rTMS onset ($P < 0.001$; Mann-Whitney U test, $P < 0.01$). Since the duration of the rTMS trains was 1.8 ± 0.5 s (supplementary motor area) and 1.9 ± 0.5 s (c-M1), stimulation over the supplementary motor area induced, on average, errors after the end of the rTMS train, while stimulation over the c-M1 induced errors during the period of stimulation.

To determine whether the timing of error induction could be a function of different stimulus intensities at a given stimulation position, we applied rTMS at 70, 80, 90, 100 and 110% of hand muscle motor threshold to the c-M1 during performance of the complex sequence (six subjects). No errors occurred at 70 and 80% of the motor threshold. Errors started to occur at 1.0 ± 0.0 s, 1.1 ± 0.5 s and 0.9 ± 0.2 s after rTMS onset for 90, 100 and 110% of the motor threshold, respectively. The end of the error induction period occurred at 2.0 ± 0.0 s, 1.6 ± 0.6 s and 2.6 ± 1.9 s after rTMS onset for 90, 100 and 110% of the motor threshold, respectively. Thus, there was no systematic shift of the timing of error induction as a function of rTMS intensity.

When the subjects were asked about their impressions of why the sequence was not played correctly (e.g. 'Was the sequence correct?'; 'Why do you think you did not play the sequence correctly? What did it feel like?'), they reported different effects for stimulation over the supplementary motor area than those for stimulation over c-M1. With c-M1 stimulation, subjects often reported jerking of the performing hand, and difficulties in executing the individual key presses

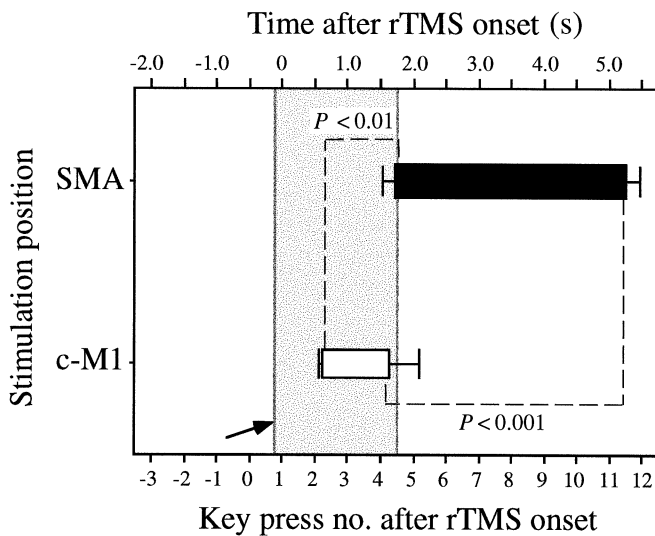


Fig. 5 Timing of error induction with stimulation over the c-M1 and supplementary motor area (SMA). The bottom time axis gives the number of the first erroneous key press after the onset of rTMS in a given sequence. The top time axis provides the corresponding values transformed into seconds (0.5 s between successive key presses, before errors occur). The rTMS trains lasted 1.8 ± 0.5 (SMA) and 1.9 ± 0.5 (c-M1) s. This implies that with stimulation over the supplementary motor area error onset occurred on average with or after the end of the rTMS train, while with c-M1 stimulation error onset fell into the intervention period (shaded area; arrow = rTMS onset). This difference was significant ($P < 0.01$; Mann–Whitney U test; 13 subjects). With c-M1 stimulation, the period during which errors occurred was essentially limited to the duration of the rTMS train, while the period of error induction extended almost to the end of the sequence with stimulation over the supplementary motor area. The timing difference of the end-points of error occurrence was significant ($P < 0.001$; Mann–Whitney U test; 13 subjects). Error bars: 1 SE for the first and last erroneous key press.

during stimulation, especially with the complex sequence. In contrast, with stimulation over the supplementary motor area during performance of the complex sequence, subjects reported that they ‘did not know anymore which series of keys to press next’, or that they ‘forgot’ the later part of the sequence, and they noted that these perceptions occurred after the end of the rTMS train rather than during stimulation. Therefore, the behavioural data also point to a qualitative difference between the effects of stimulation over the supplementary motor area and the c-M1.

Control experiment 1: EMG activity during rTMS

Stimulation over the supplementary motor area and c-M1 induced a similar number of accuracy errors during performance of the complex sequence in the six subjects tested (7.7 ± 3.0 errors with c-M1 stimulation and 9.3 ± 2.9 errors with supplementary motor area stimulation, Wilcoxon, $P > 0.2$, not significant). However, only stimulation over the c-M1 elicited a significant number of MEPs in the right extensor digitorum communis (0.5 ± 0.8

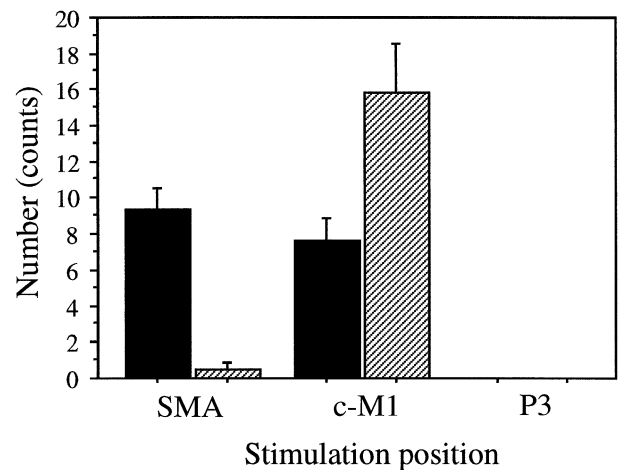


Fig. 6 Control experiment 1. Data from six subjects. The number of errors (solid bars) induced (group average) with stimulation over the supplementary motor area (SMA) is similar to that induced with stimulation over the c-M1. In contrast, while MEPs (hatched bars) were always present when errors occurred during stimulation over the c-M1, no significant number of MEPs occurred with stimulation over the supplementary motor area. Neither MEPs nor errors were present with stimulation over P3 (control position over the parietal cortex). Error bars: 1 SE.

MEPs per sequence with stimulation of the supplementary motor area and 15.8 ± 6.6 with c-M1 stimulation, Wilcoxon, $P < 0.05$). Stimulation over P3 did not result in a significant number of accuracy errors or MEPs. This indicates that the effects of stimulation over the supplementary motor area were not related to indirect stimulation of the c-M1. Figure 6 summarizes the relationship between stimulation position, number of accuracy errors and the number of MEPs.

MEPs in the tibialis anterior were observed occasionally with stimulation over the supplementary motor area, but not with other stimulus positions. There was no obvious correlation between the tibialis anterior-EMG pattern and the number of errors induced during rTMS.

Control experiment 2: effects of rTMS repetition

When rTMS was repeatedly applied over the supplementary motor area at inter-train intervals of ~1 min, the number of accuracy errors induced tended to decrease in subsequent trials. The inverse correlation between trial number and number of accuracy errors was significant ($r^2 = 0.273$, ANOVA, $F = 16.1$, $P = 0.0002$). This effect was present with stimulation over the supplementary motor area, but not over the c-M1 ($r^2 = 0.028$, ANOVA, $F = 0.7$, $P = 0.4$), indicating that the effect was not due to adaptation to nonspecific factors such as attention or discomfort, but rather was linked to certain properties of the supplementary motor area. Figure 7 shows the results of the simple regression analysis.

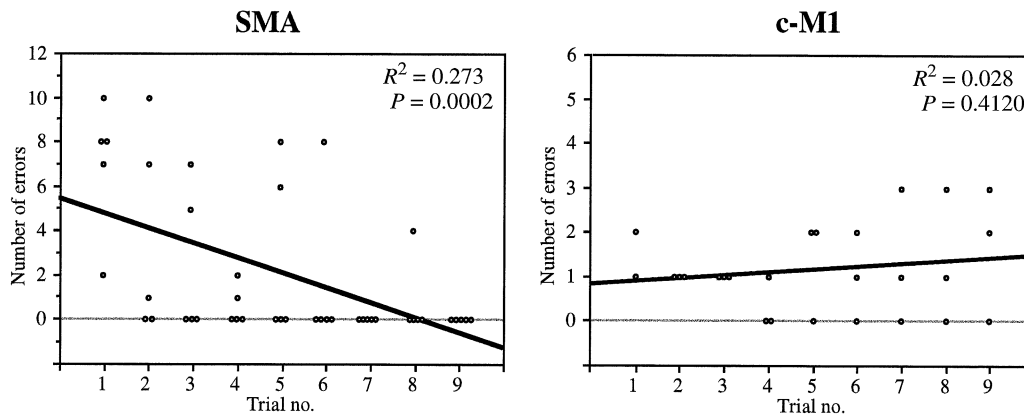


Fig. 7 Control experiment 2. Individual data from five subjects (SMA) and three subjects (c-M1). Effects of repeated application of rTMS over the supplementary motor area (SMA) and c-M1 in nine subsequent trials within one experimental session. Note the significant inverse correlation between number of accuracy errors and trial number when rTMS was given over the supplementary motor area, but not when rTMS was applied over the c-M1. The time between Trial 1 and Trial 9 was ~10–15 min.

Discussion

Our results show that rTMS applied over the mesial frontocentral cortex, which includes the supplementary motor area, interfered with the organization of future components in a complex movement sequence. This pattern of disturbance was significantly different from that observed with stimulation over the c-M1, in which errors were induced during the period of rTMS interference, in both complex and simpler movement sequences. This finding of a differential effect of rTMS over the supplementary motor area and the c-M1 suggests that functional integrity of the supplementary motor area is particularly critical for the organization of future components in complex sequential finger movements.

Magnetic stimulation

The nature of rTMS is such that it can interfere regionally with cortical function, as shown in studies involving the visual system, language processing, a recall paradigm (Pascual-Leone *et al.*, 1991, 1994a; Grafman *et al.*, 1994) and, more recently, with motor sequence processing in the primary motor cortex (Corwell *et al.*, 1996; Chen *et al.*, 1997). The concept of rTMS interference comes closest to inactivation studies in animals, or to some extent the preoperative sodium amobarbital test (Wada's test), but rTMS has the advantage of being noninvasive and of much more discrete and limited duration. As opposed to functional imaging and EEG, which show activation of areas 'associated' with a certain task, inactivation techniques can detect which areas are 'necessary' for the successful completion of a task. We assume that (i) the probability of disturbing a task performance with rTMS becomes higher the more functionally relevant a stimulated area is and (ii) that the type of 'deficit' induced reflects to some extent how the stimulated area normally contributes to the task performance.

A major question is which anatomical structures were in fact stimulated when rTMS was applied to the frontocentral

midline, and to what extent were they stimulated? Besides the two portions of the right and left supplementary motor area (supplementary motor area proper and pre-supplementary motor area; mesial Brodmann area 6), other structures possibly stimulated were the cingulate motor areas (Brodmann areas 24, 23, 32, 31) of both hemispheres. We used TMS-induced leg-muscle activation from the standard Cz position to determine an appropriate scalp position for stimulating the supplementary motor area (Fig. 8). The rationale for this procedure was that leg representations in the supplementary motor area and the primary motor cortex are located in adjacent positions and at a similar depth within the interhemispheric fissure. It is impossible to measure the field strength and its local 'effectiveness' upon supplementary motor area neurons in the human brain directly and noninvasively. However, it is possible to use available modelling data to approximate the decrease of field strength from superficial to deeper cortical areas. Figure 8 shows the relationship between the anatomy of the mesial cortex and the shape of the magnetically induced electric field, as estimated on the basis of model measurements that have been carried out previously for a circular magnetic coil (Roth *et al.*, 1991; *see also* Maccabee *et al.*, 1991). Based on these anatomical and physical data, we propose that the mesial area 6 (supplementary motor area) was the main locus of effective stimulation in the present study, probably the supplementary motor area proper more than the pre-supplementary motor area because the supplementary motor area proper is closer to the Cz position and to the primary motor cortex leg representation, which was our physiological reference. It is much less likely that we exerted effective field strengths on the cingulate gyrus (areas 24, 23, 32, 31) due to its deeper location (compared with that of the supplementary motor area) within the interhemispheric fissure. According to the model, at a given stimulus intensity, the field strength in the cingulate gyrus should be ~18%–29% of the one at the depth of the supplementary motor

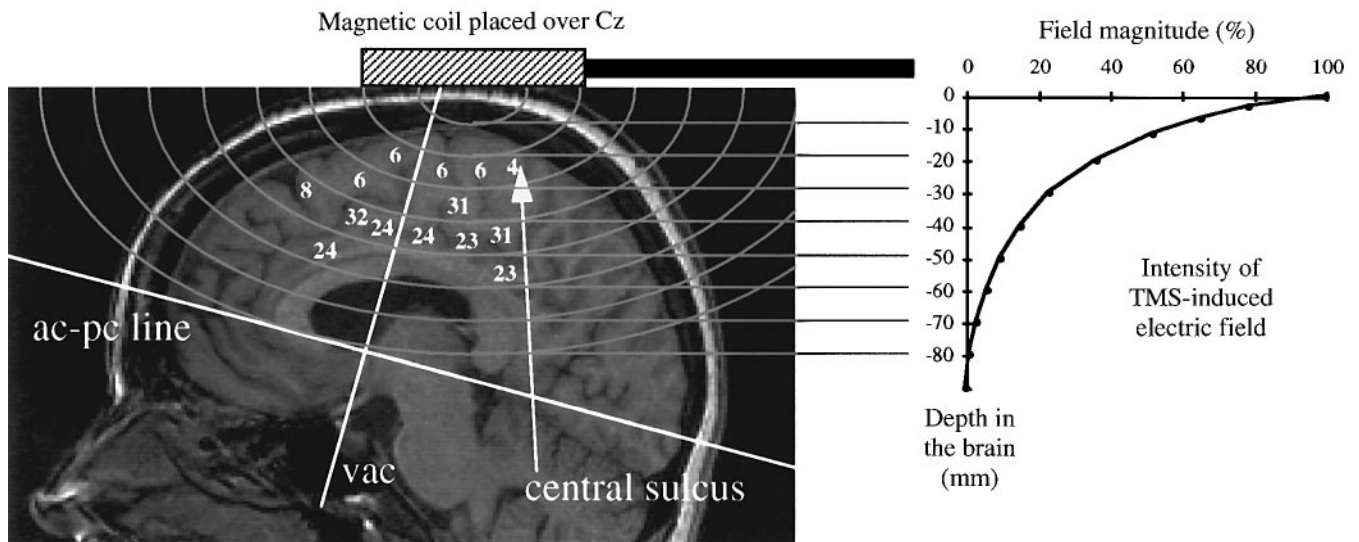


Fig. 8 The relationship between the anatomy of the mesial cortex and the shape of the magnetically induced electric field as estimated on the basis of model measurements (Roth *et al.*, 1991). T₁-weighted conventional magnetic resonance image (sagittal slice, 1.5 Tesla) of a normal subject. The numbers refer to Brodmann areas. Area 6 represents the supplementary motor area, areas 24, 32, 23, 31 the cingulate cortex, area 4 the primary motor cortex representation of the leg, and area 8 the prefrontal association cortex. The vertical anterior commissure line (vac) crosses the anterior commissure and is orthogonal to the anterior commissure–posterior commissure (ac-pc) line. The vac line roughly separates pre-supplementary motor area (anterior to vac) and the supplementary motor area proper (posterior to vac). The arrow marks the central sulcus. The magnetic coil is positioned over Cz in this figure, and the concentric lines represent electric field lines of different field magnitudes. The field magnitudes for each line can be identified in the graph on the right side where the field magnitudes are plotted as a function of the depth inside the brain. Note the substantial difference in estimated field magnitudes between the supplementary motor area and the cingulate cortex (3–5 times greater field magnitudes in the more superficially located supplementary motor area). According to these considerations, even taking into account inter-individual anatomical variability, the supplementary motor area is the most likely target region when rTMS is applied over Cz.

area. The relative stimulus intensity in the supplementary motor area should, therefore, be three to five times as high as the one in the cingulate gyrus. Approximately the same holds true for unintended stimulation of more anteriorly located frontal regions such as area 8 (see Fig. 8). The approach used does not allow for discrimination of unilateral and bilateral supplementary motor area stimulation, and it seems likely that we stimulated the supplementary motor area bilaterally.

Another possible question is whether high-intensity rTMS of the supplementary motor area could result in indirect orthodromic stimulation of the lateral area 4 (i.e. c-M1). However, our results and previous data indicate that this is unlikely. First, direct stimulation of the c-M1 that was ineffective in eliciting MEPs in muscles of the performing hand never induced sequence errors (Corwell *et al.*, 1996), while stimulation over the supplementary motor area consistently induced errors in the absence of MEPs (Control experiment 1). Secondly, rTMS over the supplementary motor area and the c-M1 resulted in different timing patterns of error induction. If the delayed error induction with rTMS over the supplementary motor area were a consequence of temporal summation of ('subthreshold') volleys from the region of the supplementary motor area to the c-M1, then (i) subthreshold stimulation directly over the c-M1 should result in a similarly late error onset, (ii) suprathreshold stimulation over the c-M1 should cause temporal summation in the c-

M1 as well and therefore result in a combination of early onset and prolonged duration of the error induction period and (iii) summation effects should also occur with stimulation over other brain regions that are as close and as densely connected to the c-M1 as the supplementary motor area, such as prefrontal and parietal areas. None of the points (i) to (iii) was true in our data. On the contrary, as soon as errors were induced by 'subthreshold' stimulation of the c-M1 (90% of the motor threshold), they occurred during and not after the period of stimulation, therefore following exactly the same pattern as with rTMS over the c-M1 at intensities of 100 and 110% of the motor threshold. Stimulation over prefrontal and parietal areas did not induce any errors (early or late).

The rTMS-induced volleys could also travel from the supplementary motor area to the lateral premotor area (area 6). The premotor area plays an important role in preparation for and sensory guidance of movements (Wise, 1985; Kurata and Wise, 1988; di Pellegrino and Wise, 1993) and in motor sequence organization (Mushiake *et al.*, 1991; Halsband *et al.*, 1993; Sadato *et al.*, 1996). This seems to be especially true for the premotor area in the right hemisphere, even when finger sequences are performed with the right hand (Sadato *et al.*, 1996). The indirect nature of stimulation experiments in humans makes it impossible to exclude the potential for some referred interference with the premotor area when the supplementary motor area is stimulated. However, it seems unlikely. First, the stimulus thresholds sufficient to elicit

motor responses by intracortical electrical stimulation are higher in the premotor area than in the primary motor cortex (Weinrich and Wise, 1982; Preuss *et al.*, 1996). That means that indirect stimulation of the premotor area is even less likely than indirect stimulation of the c-M1. Secondly, if the lateral premotor area could be stimulated so easily and if premotor area dysfunction were the major mechanism responsible for the induced errors, then lateral c-M1 stimulation with the coil much closer to the premotor area should also act on the premotor area. In this case, we would again expect similar disturbance patterns with stimulation over the c-M1 and supplementary motor area, which was not the case.

In the present study, the group-averaged onset of error induction with stimulation over the supplementary motor area coincided largely with the end of the rTMS train. Could the late error onset have been related to the 'turning off' of the current in the magnetic coil? This is unlikely, for at least two reasons: (i) in some cases the error onset with stimulation over the supplementary motor area occurred prior to the end of the rTMS train (*see* Fig. 5) and (ii) rTMS studies so far provide only evidence for effects related to 'turned on' currents in the coil (Chen *et al.*, 1997; Pascual-Leone *et al.*, 1994b).

In previous experiments (Corwell *et al.*, 1996; Chen *et al.*, 1997), we have shown that peripheral stimulation of forearm muscles of the performing hand, deprivation of visual or acoustic feedback, and attenuation of sensory feedback cannot account for the induction of errors in these overlearned finger sequences. Non-specific rTMS effects such as interference with global attention due to noise or discomfort cannot explain the results of stimulation over the supplementary motor area and the c-M1 either, since stimulation over other scalp positions (e.g. F3, FCz, P3) did not result in error induction. As for F3 and P3, this should, on the other hand, not be interpreted as evidence for inactivity of parietal or prefrontal regions in our paradigm, since the susceptibility of these areas to stimulation may be lower than the one of the c-M1 (Amassian *et al.*, 1991).

In summary, our data point to regional interference with the function of the supplementary motor area as the most likely mechanism to explain the effects of stimulation over the frontocentral midline.

Role of the supplementary motor area for sequential finger movements

Organization of movement sequences of different complexity

Our data are in keeping with those of previous studies showing that the supplementary motor area plays an important role in the preparation and performance of sequential movements, especially when they are retrieved from memory (Lang *et al.*, 1988; Mushiake *et al.*, 1990, 1991; Halsband *et al.*, 1993; Rao *et al.*, 1993; Shibasaki *et al.*, 1993; Tanji,

1994; Tanji and Shima, 1994, 1996; Hikosaka *et al.*, 1996; Sadato *et al.*, 1996). In the present study, stimulation over the supplementary motor area caused errors only in the most complex sequence. We conclude, therefore, that the supplementary motor area was more active and more critically involved in processing the complex sequence than the simpler ones. It is possible that higher stimulation intensities over the supplementary motor area (which could not be used for safety and technical reasons) might have been sufficient to interfere with simpler sequences as well. Our conclusion, however, would still be the same, since we do not state that the supplementary motor area is inactive or functionally irrelevant for the performance of simple sequential movements.

That the supplementary motor area is particularly involved in processing complex sequences is well supported by PET and fMRI findings, as well as by EEG data, in humans. Using PET, Orgogozo and Larson (1979) found increased rCBF (regional cerebral blood flow) in the supplementary motor area associated with various complex voluntary movements. Shibasaki *et al.* (1993) compared simple simultaneous oppositions of fingers 2–5 to the thumb with a more complex sequential finger opposition task (fingers 2–2–3–4–4–4–5–5 to the thumb and reverse), and observed higher rCBF increases in the supplementary motor area with complex than with simple finger movements. Using fMRI, Rao *et al.* (1993) also showed that more complex sequential finger movements (tapping the tips of fingers 3–5–4–2 on a flat surface) were associated with a higher degree of supplementary motor area activation than simpler finger movements (simultaneous tapping of fingers 2–3–4–5 on a flat surface). This relative difference was found for both self-paced and metronome-paced movements. Lang *et al.* (1989) also found that amplitudes of the slow negative electrical activity during performance of complex movements were increased, compared with simple movements, in EEG scalp electrodes located over the supplementary motor area region. In addition to these previous findings, we now demonstrate that the human supplementary motor area appears to be a 'necessary' component in the motor network that is involved in processing forthcoming elements of complex movement sequences.

Movement complexity might be understood in a variety of ways. Not only factors such as speed and accuracy, and involvement of different muscles (Colebatch *et al.*, 1991) and joints (Ghez *et al.*, 1991; Martin and Ghez, 1993), but also the degree of experienced practice (Karni *et al.*, 1995; Pascual-Leone *et al.*, 1995), or different modes of movement selection (Lang *et al.*, 1989; Shibasaki *et al.*, 1993; Sadato *et al.*, 1996) or movement preparation (Alexander and Crutcher, 1990a, b; Georgopoulos, 1994; Kawashima and Fukuda, 1994; Kawashima *et al.*, 1994) can contribute to movement complexity. The term complexity is used in the present study simply to describe different degrees of difficulty in acquiring and playing the sequences without errors on the piano. These differences in complexity were reflected in the

different acquisition times necessary to reach the required performance level for each sequence. We focus here on the difference between the scale and the complex sequences, since simple index finger tapping (simple condition) was not disturbed in any of the stimulation conditions. Both the scale sequence and the complex sequence were overlearned so that the accuracy had to be 100% in 10 subsequent pre-rTMS trials, and were always played with the right hand (which was kept in a consistent position for all conditions), with the same speed and rhythm. In addition, the number of key presses per finger and sequence was matched to avoid any bias due to the use of different fingers. These two sequences differed clearly with respect to the order of key presses. The higher degree of difficulty in the complex sequence resulted from a less natural flow of subsequent movements, involving jumps over one or two keys (2–5, 3–5 and so on) instead of playing only adjacent keys always in the same direction (5–4–3–2, 5–4–3–2 and so on), as in the scale sequence. Therefore, the fact that stimulation over the supplementary motor area interfered only with the complex sequence is attributed to its higher complexity in terms of element selection and composition. Sequence length as an additional complexity element was inherent in our paradigm and may also have contributed to the total complexity and the differences between sequences.

All sequences in the present study were metronome-paced to assure that the number of keypresses prior to and during stimulation was constant across trials and across individuals. Fast rhythmical, metronome-paced movements as an example of externally cued movements are peculiar in that they do not actually require 'reaction' to each external stimulus, particularly not once they are well learned (cf. Obeso *et al.*, 1995). Due to the regularity and relatively fast rate of the rhythm, the tones are anticipated and the metronome is used only as 'pacemaker'. Behaviourally, this results in a phenomenon called 'negative asynchrony' (Aschersleben and Prinz, 1995), that is, the fact that movement onset precedes the corresponding metronome beats. That the supplementary motor area is significantly involved in the generation of this type of overlearned sequential movement, as our data suggest, has been documented in previous PET (Shibasaki *et al.*, 1993; Sadato *et al.*, 1996; Hazeltine *et al.*, 1997) and fMRI studies (Rao *et al.*, 1993; Hikosaka *et al.*, 1996). Recent data even suggest that at least the posterior part of the supplementary motor area (supplementary motor area proper) is similarly active during internally generated and true externally instructed movements (Deiber *et al.*, 1996).

Organization of future movements

Our data are consistent with a view of the supplementary motor area as an area that combines elements of pre-planned movement sequences into clusters of a feasible size, and sends them, for example, 'chunk-by-chunk' (Adams, 1984; Verwey, 1996), to other motor regions, particularly to the primary motor cortex, where they are executed. With respect

to the timing of error induction, this would predict our present results very well, namely, (i) that disturbance of primary motor cortex function affects ongoing motor performance during stimulation, whereas 'future chunks' that have not yet arrived in the primary motor cortex can be properly executed; and (ii) that disturbance of supplementary motor area function does not interfere with ongoing performance during stimulation (because these motor sequence elements have already been processed in the supplementary motor area and been sent to other motor areas such as the primary motor cortex), but it does interfere with future chunks (i.e. blocks of upcoming movements in a motor sequence).

On average, the first error induced with stimulation over the supplementary motor area occurred ~1 s (or two key presses) later than that induced with stimulation over the c-M1. We conclude, therefore, that the supplementary motor area is necessary for the organization of upcoming movements in a complex motor sequence. A similar conclusion was proposed by Tanji and Shima (1994), who found cells in the monkey supplementary motor area, but not in the c-M1, whose activity was related to a sequence of movements that were performed in a particular order (e.g. 'push-pull-turn'). The activity in these neurons was preparatory and preceded single movements by one or more seconds. Some of these cells were predominantly active in relation to a particular order of the upcoming total sequence, and others were preferentially active during the interval between two specific movements, that is, for example, in the waiting interval between push and pull, but not between pull and push. The authors concluded that these two groups of cells contribute a signal about the order of forthcoming multiple movements and are useful for planning and coding of several movements ahead. This type of activity was found only when the movement sequences had to be rehearsed from memory, not when each movement in the sequence was determined on-line by a visual cue (*see also* Mushiake *et al.*, 1990). The pacing was acoustic in all movement conditions in these experiments, which are therefore comparable to our paradigm.

In regard to non-invasive electrophysiological data in humans, it has been suggested that the 'Bereitschaftspotential' (readiness potential) reflects preparatory activity of the supplementary motor area prior to voluntary movements (Kornhuber and Deecke, 1965; Deecke and Kornhuber, 1978; Lang *et al.*, 1991; Knosche *et al.*, 1996). The Bereitschaftspotential starts ~1.5 s before movement onset, indicating that an upcoming movement may be prepared in the supplementary motor area well in advance. The late part of the Bereitschaftspotential (the so-called NS') is thought to reflect activity of the c-M1 that follows the onset of supplementary motor area activation by ~1 s (Barrett *et al.*, 1986). According to this, one would predict that effects of stimulation over the supplementary motor area on motor performance should occur ~1 s later than with stimulation over the c-M1, which was in fact the case in the present study.

Another interesting finding in our experiment was that subjects only reported that they 'did not know anymore

which series of keys to press next' with stimulation over the supplementary motor area (but not over c-M1). This reminded us of reports of Fried *et al.* (1991), who stimulated the supplementary motor area (at rest) electrically through subdural grid electrodes. Their patients reported an 'urge' to perform a movement or 'anticipated' that a movement was going to occur. Both sets of reports support the idea of the relevance of the supplementary motor area for the composition of future movements. It seems as if both 'forced retrieval' of motor programs and 'disruption' of ongoing motor programs can be induced by supplementary motor area stimulation, depending on the stimulus type and intensity.

Taken together, our data are consistent with serial processing steps in the supplementary motor area and c-M1. It needs to be emphasized, however, that we do not interpret our results as evidence against parallel processing in these areas. The functional role of the supplementary motor area is probably far more complicated, integrating both serial and parallel operating modes, and our present data reflect only one, yet an important, aspect of it. In fact, there is clear evidence for parallel changes of subdurally recorded EEG activity in the supplementary motor area and c-M1 prior to single movements (Ikeda *et al.*, 1992, 1993, 1995). Thus, the mode of operation in the cortical motor system may also be highly dependent on the specific task demands.

Compensation for rTMS interference with supplementary motor area function

In the present study, we found characteristic changes in motor behaviour for a situation of acute short-lasting interference with supplementary motor area function. We also observed that the number of errors induced by rTMS over the supplementary motor area decreased when rTMS trains were administered repeatedly in subsequent trials over a period of 10–15 min. Regarding this observation, it could be of importance that there appears to be an extraordinary restorative potential of the brain to compensate almost completely (and very rapidly) for supplementary motor area lesions (Laplaine *et al.*, 1977; Brinkman, 1984; Tanji, 1994). Even after large corticectomies, including the supplementary motor area, patients can recover substantially or completely from early postoperative motor deficits within <1 month after the operation (Laplaine *et al.*, 1977; Zentner *et al.*, 1996). In our experiment, we probably mimicked a small and transient supplementary motor area lesion. One might therefore speculate that the inverse correlation of trial number and error rate reflects fast compensatory mechanisms. The trigger for this compensation could be the repeated experience that the supplementary motor area does not function normally (temporarily mimicking a 'lesion') and that other strategies are necessary to achieve the behavioural goal. This inverse correlation was specific for rTMS over the supplementary motor area, and did not occur with c-M1 stimulation. Therefore, adaptation to nonspecific factors (e.g. attention,

discomfort) cannot explain the effect. Rather, it is a consequence of how the supplementary motor area, in particular, is flexibly integrated into the motor control network that is used for the implementation of complex sequential finger movements.

Conclusion

The present findings argue for a critical role of the human mesial frontocentral cortex, most likely the supplementary motor area, in the organization of forthcoming movements in complex motor sequences that are rehearsed from memory and fit into a precise timing plan.

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