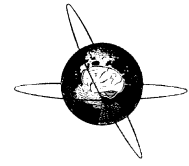




ELSEVIER

Clinical Neurophysiology 115 (2004) 145–153



www.elsevier.com/locate/clinph

Functional lesions and human action monitoring: combining repetitive transcranial magnetic stimulation and event-related brain potentials

Jens D. Rollnik^a, Christine Schröder^a, Antoni Rodríguez-Fornells^{b,c}, Arthur R. Kurzbuch^b, Jan Däuper^a, Jörn Möller^b, Thomas F. Münte^{b,*}

^aDepartment of Neurology, Medizinische Hochschule Hannover, Hannover, Germany

^bDepartment of Neuropsychology, Otto von Guericke University, Universitätsplatz 2, Gebäude 24, 39106 Magdeburg, Germany

^cFaculty of Psychology, University of Barcelona, Spain

Accepted 8 May 2003

Abstract

Objective: Electrophysiological recordings of the error-related negativity (ERN) and functional imaging data point to an involvement of medial frontal cortex (including the anterior cingulate cortex, ACC) and dorsolateral prefrontal cortex (DLPFC) in the detection and correction of performance errors. Here, we studied this network by applying trains of rapid transcranial magnetic stimulation (rTMS) prior to the recording of the ERN.

Methods: Low-frequency (0.9 Hz) rTMS was applied to medial frontal or lateral frontal regions (different sessions) for 60 s immediately before each 3 min ERN recording in 11 healthy young subjects. The ERN was obtained by multichannel recordings in a typical Eriksen flanker task with instructions calling for immediate error correction in case a performance error was detected by the subject. Event-related potentials were quantified and statistically evaluated using standard methodology.

Results: Compared to a no-stimulation control condition, medial frontal stimulation led to a small but reliable decrease in the number of corrected errors as well as to an attenuation of the ERN and an increase of the subsequent error-positivity (Pe). No effect on these components was seen after lateral frontal stimulation. No reliable effects on the lateralized readiness potential were observed.

Conclusions: Functional lesions by rTMS appear to interfere with the functions of the medial frontal cortex in error detection and correction.

© 2004 International Federation of Clinical Neurophysiology. Published by Elsevier Ireland Ltd. All rights reserved.

Keywords: Transcranial magnetic stimulation; Error related negativity; Prefrontal cortex; Error detection; Error correction

1. Introduction

The ability to monitor complex cognitive and motor tasks, to compare one's actual behavior to the desired outcome, and to detect and correct performance errors is a prerequisite for successful performance. Surprisingly, however, after a brief period of attention devoted to self monitoring and error detection in the sixties (Angel et al., 1970; Rabbitt, 1966a,b, 1968; Rabbitt and Phillips, 1967), interest in action monitoring has been revitalized only over the last few years.

At least 3 different processes are engaged by a subject when faced by a performance lapse: error detection, error

correction and error compensation (Cohen et al., 2000; Gehring et al., 1995; Rodríguez-Fornells et al., 2002; Scheffers et al., 1996). The last two processes refer to the remedial actions implemented by the organism: error correction implies immediate-fast corrections of the erroneous responses, whereas error compensation applies to remedial actions elicited in order to avoid future error responses (e.g. slowed reaction times in the next trials). A priori, it seems logical that error detection and error correction should be strongly related and interconnected processes but little is known about their interaction.

1.1. The electrophysiology of human action monitoring

Using the event-related brain potential (ERP) technique, a specific component has been identified, labeled as Error

* Corresponding author. Tel.: +49-391-671-8469; fax: +49-391-671-1947.

E-mail address: thomas.muente@med.uni-magdeburg.de (T.F. Münte).

related negativity (ERN) (Gehring et al., 1995) or Ne (Falkenstein et al., 1995). This is obtained by computing ERP averages time-locked to the subject's response. The peak amplitude of the ERN is observed approximately 60–100 ms after incorrect responses, is maximal when accuracy is stressed, and appears to be present only when the error is consciously detected (Bernstein et al., 1995; Christ et al., 2000; Coles et al., 1995; Elton et al., 2000; Falkenstein et al., 1991, 1995, 2000; Gehring et al., 1995; Holroyd et al., 1998; Luu et al., 2000a,b; Scheffers et al., 1996, 1999; Scheffers and Coles, 2000). Immediately after the ERN a positive component emerges, which is called the error positivity (Pe). This Pe component shows a maximum at centro-parietal sites in the range of 200–300 ms (Davies et al., 2001; Falkenstein et al., 2000).

Dipole modeling analysis of the ERN showed a major contribution of a medial frontal generator (usually ascribed to anterior cingulate cortex, ACC) (Dehaene et al., 1994; Miltner et al., 1998; Ullsperger and von Cramon, 2001) but better fits can be obtained when additional lateral sources are introduced (Luu and Tucker, 2001). ACC activity in error processing has also been observed using single-unit recordings from monkeys (Niki and Watanabe, 1979).

Electrophysiological findings regarding the ERN have usually been interpreted as being a physiological reflection of an error detection process proper (i.e. the more salient an error is, the more pronounced will be the ERN emanating from the ACC) (Falkenstein et al., 2000; Holroyd and Coles, 2002). However, the ERN has also been discussed as reflecting emotional and motivational information carried by the error (Bush et al., 2000), as well as reflecting response conflict (Botvinick et al., 2001; Carter et al., 1998; Gehring and Fencsik, 2001; Van Veen et al., 2001). The latter account fits well with findings showing ERN like activity in correct trials (Coles et al., 2001; Luu et al., 2000a, b; Scheffers and Coles, 2000; Vidal et al., 2000).

The relation of the ERN to corrective behavior has been addressed recently (Rodríguez-Fornells et al., 2002). By comparing the timing of the ERN with the onset characteristics of the lateralized readiness potential (LRP), an index of the preparation of a motor response, in experiments that either did or did not require the correction of performance errors it was shown that the ERN occurs later than or, at best, in parallel to the initiation of the corrective response. These data therefore suggest, that the process underlying the generation of the ERN can not be the one initiating the corrective response.

The interpretation of the Pe component is still controversial. Because its resemblance to the P3b component, some authors have proposed that it might be an internally generated P3b component which follows the detection of the error and thus the ERN. This view is supported by a study that did not find differences in the topographical distribution of the Pe component and the P3b component seen in the correct trials (Davies et al., 2001). Other authors, however, have found that Pe and P3b are affected differently by some

experimental manipulations, suggesting that both components are reflecting different cognitive processes (Falkenstein et al., 2000). One recent interpretation is that this component is indexing the degree of awareness that an error has been committed (Nieuwenhuis et al., 2001; Vidal et al., 2000), while others have pointed out that the Pe component might index the subjective or emotional significance of the error (Falkenstein et al., 2000).

1.2. *The anatomy of human action monitoring*

Medial and dorsolateral prefrontal cortex has also been implicated in action monitoring by functional imaging studies. For example increased activity in the ACC (ACC, Brodmann areas 24/32) has been found for incorrect responses (Carter et al., 1998; Kiehl et al., 2000; Menon et al., 2001; Ullsperger and von Cramon, 2001). More evidence for a role of the ACC in action monitoring comes from a series of functional magnetic resonance imaging (fMRI) studies (Botvinick et al., 1999; Carter et al., 1999, 2000; Cohen et al., 2000; MacDonald et al., 2000; Van Veen et al., 2001). The ACC activations in fMRI studies (extending to Stroop and other interference paradigms) have been thought of as reflecting 'response competition' (i.e. the more competition between several available response alternatives, the more pronounced the activation in the ACC). Garavan et al. (2002) noted that the midline area activated by errors more than by correct trials is quite large and incorporates both the ACC and, more superiorly, the pre-SMA. Ullsperger and von Cramon (2001) found these same areas but suggested that response competition and error processing can be dissociated and assigned to adjacent medial frontal areas. They suggest that the cingulate motor area (CMA, BA 24c) plays a role in error detection, while response conflict monitoring appears to be implemented in a larger area of the frontomedian wall, i.e. the pre-SMA.

Several of the neuroimaging studies have also shown activation in lateral frontal cortex in addition to the ACC (Kiehl et al., 2000; MacDonald et al., 2000; Menon et al., 2001), evidence that fits well with source models of the ERN (Luu and Tucker, 2001).

1.3. *Patient data*

These neuroimaging findings call for a test using patients with lesions to parts of the putative action monitoring network. In a first study, Gehring and Knight (Gehring and Knight, 2000) tested patients with lesions to the lateral frontal cortex in a letter discrimination flanker task while their ERPs were recorded. Compared to normal controls, the ERN of the patients to error trials was not reduced. Rather, a similar deflection was observed for correct responses as well. Likewise, Ullsperger et al. (2002) found no differences between erroneous and correct responses regarding the ERN component in patients with lateral prefrontal lesions.

Patients with orbitofrontal or temporal lesions in the Ullsperger et al. (2002) study did not show any changes in the ERN and its morphology. A common finding has thus been that correct and erroneous responses showed the same amplitude regarding the ERN in patients with lateral frontal lesions, suggesting that the lateral prefrontal cortex is involved in the process of discriminating between correct and erroneous responses.

In several groups of patients with lesions in the ACC the ERN has been found to be missing or greatly attenuated (Segalowitz et al., 2000; Stemmer et al., 2000; Swick and Turken, 2002; Turken and Swick, 1999).

1.4. The present study

Taken together, at present there are only very few electrophysiological and no neuroimaging studies available on patients with lesions or functional disturbances of the putative action monitoring network that can be used to cross-validate the data obtained in normal controls. Moreover, lesions of patients and consequently their performance is notoriously variable. In the present project we therefore employed event-related brain potentials in an action monitoring task in conjunction with repetitive transcranial magnetic stimulation (rTMS) that allows to induce temporary partial functional lesions in normal subjects.

Transcranial magnetic stimulation allows a non-invasive stimulation of the cerebral cortex (Barker et al., 1985). In particular, rTMS can be used to interfere with various functions of the central nervous system and has gained increasing popularity in cognitive neuroscience (Jahanshahi and Rothwell, 2000; Pascual-Leone et al., 2000; Walsh and Cowey, 2000). Depending on the stimulation frequency, a temporary activation or inhibition of selected cortical areas may be achieved. While high stimulation frequencies (5 Hz or 20 Hz, for instance) are able to activate (Pascual-Leone et al., 1998; Rollnik et al., 2000b, 2001), low-frequency rTMS (e.g. 0.9 Hz) has been shown to produce inhibition of cortical areas (Chen et al., 1997; Maeda et al., 2000; Pascual-Leone et al., 1998). For example, Chen and co-workers have used a 15 min 0.9 Hz rTMS train and found a decrease of motor cortex excitability lasting 15 min after the end of the stimulation (Chen et al., 1997). In the present study, employing a paradigm similar to the one used by Rodriguez-Fornells et al. (2002), we applied inhibitory rTMS to medial and lateral frontal cortex, i.e. to sites that have been identified in previous neuroimaging and electrophysiological studies as being important for error monitoring. We were thus able to compare subjects' behavior and ERP responses while 'suffering' from different functional lesions with their normal behavior.

It is of interest to note that medial frontal cortex has been targeted by a number of previous rTMS studies. For example, Jahanshahi et al. (1998) applied rTMS over the medial frontal cortex in a classical random number generation paradigm and reported an effect in some but

not all subjects. More consistent results were reported by Hadland et al. (2001) who investigated behavioral effects of rTMS to the dorsolateral prefrontal and the medial frontal cortex in a task requiring the subjects to decide themselves what action to perform with their fingers. They found that stimulation of both regions interfered with the performance in the 'free selection' condition but not in a control condition. Hadland et al. (2001) pointed out that their medial frontal cortex stimulation definitely targeted the posterior pre-SMA and the anterior part of the SMA, i.e. regions suspected to be involved in error processing in fMRI tasks (e.g. Garavan et al., 2002), while they found it less clear whether effective interference was achieved in the underlying cingulate sulcus. Also, Gerloff et al. (1997) reported that rTMS over the medial frontal cortex led to an increase in accuracy errors in a task that required the reproduction of complex sequences of learned finger movements.

2. Methods

The study was conducted with the approval of the local institutional review board.

2.1. Subjects

Eleven right-handed neurologically healthy students participated in the experiment (4 women; mean age \pm SD, 24.6 \pm 4.5 years) after informed consent according to the declaration of Helsinki. They were paid for their participation.

2.2. Stimuli and procedure

A typical Eriksen flankers task (Eriksen and Eriksen, 1974) was used. Subjects were required to focus on the letter in the center of a 5 stimulus array (H or S), designated as 'target,' and to make a choice reaction-time response, e.g. to press a button held in the left hand for an 'S' and a right-hand button for an 'H.' Moreover, in case that they detected an error they were encouraged to correct their response as fast as possible. The flanker-letters surrounding the target letter either favored the target response (compatible trials, HHHHH or SSSSS) or primed the other response (incompatible trials, HSHSH or SSHSS). To optimize the number of errors produced 40% of compatible trials and 60% of incompatible trials were presented. Each stimulus array subtended about 2.5° of visual angle in width, and a fixation line was presented in the middle of the computer monitor just below the target letter in the array. Duration of the stimuli was 100 ms. A fixed SOA of 900 ms was used. This SOA was determined in pilot experiments to be optimal for the elicitation of the ERN component. Letter/hand assignments were counterbalanced between subjects and maintained in both sessions.

The current study used an individual reaction time (RT) deadline that was determined as described earlier (Rodriguez-Fornells et al., 2002). Subjects were first trained with 200 trials to reach a reaction time (RT) baseline level that was used as a starting point to fix the RT deadline. Then, after each of 6 series comprising 40 trials subjects received feedback about their performance. Whenever subjects had less than 15% of errors, they were told to react faster and an adjustment to the deadline was made. After this procedure the experiment proper began. In each session the subjects first received 9 blocks of 200 trials without prior rTMS. These were followed by 15–20 blocks of 3 min duration that were immediately preceded by 60 s of rTMS as described below. In one session subjects received rTMS to the right lateral frontal cortex and in the other session the medial frontal cortex was stimulated. The order of stimulation sites was counterbalanced across subjects.

2.3. rTMS

Inhibitory rTMS (frequency of 0.9 Hz) was performed with a MagstimRapid device (The Magstim Company, Whitland, UK) and a figure-of-8 coil. On the initial visit, the motor threshold (MT) of the left abductor pollicis brevis muscle was determined (George et al., 1997). MT was defined as lowest intensity which produced 3 responses with an amplitude of at least 50 μ V in 4 trials (Rollnik et al., 2000a). Mean MT in our sample was 50.1% (SD 7.9) of maximum stimulator output corresponding to 1 T. To achieve intersubject consistency of stimulation sites, these were defined with regard to the International 10–20 system for EEG recording sites (Steinmetz et al., 1989). The medial frontal stimulation site was located between Fz and Cz, while the right lateral frontal site was located halfway between F8 and T8. To verify the anatomical positions stimulated, we performed the following measurements in 4 additional subjects who had not participated in the rTMS/ERP study. The stimulation coordinates as defined by the 10–20 system as well as 5 anatomical landmarks (2 pre-auricular points, nasion,inion, vertex) were digitized using a Polhemus Fastrak II (Polhemus Inc., Colchester, VT). These coordinates were co-registered with the individual high-resolution 3-dimensional (3D) T1-weighted MRI scans using the 'MRICro' and 'MRIreg' software packages by Chris Rorden (<http://www.cla.sc.edu/psyc/faculty/rorden/>). Using these programs, the stimulation positions were transferred onto the individual MRIs. Subsequently, these images were normalized and superimposed by an overlay containing the Brodmann areas.

This procedure indicated that the medial frontal stimulation site was directly over the anterior part of Brodmann area 6, i.e. the pre-SMA, while the lateral stimulation site was over the junction of areas 44, 45 and 46. Fig. 1 gives an example for the localization of the stimulation sites. Prior to each ERP-block, 60 s trains of 0.9 Hz at 90% of MT (subthreshold) were applied to these defined sites.

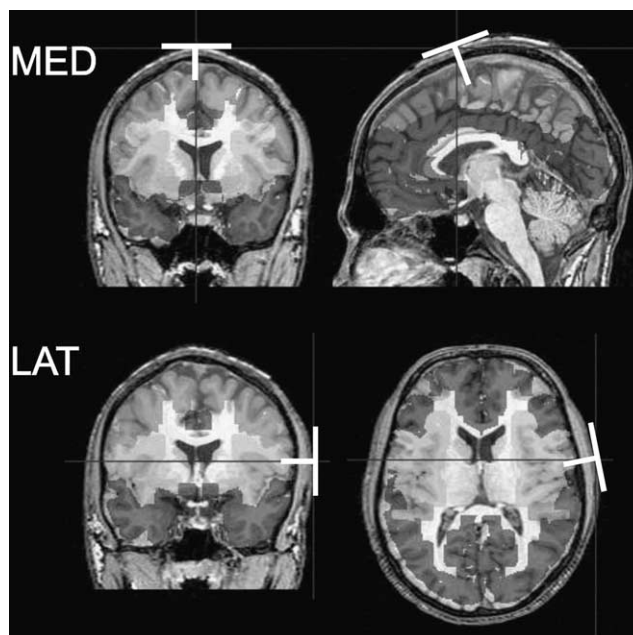


Fig. 1. Illustration of the anatomical stimulation sites. Stimulation sites were defined by the 10–20 system and verified by matching their digitized coordinates with the individual 3D high-resolution T1-MRI as described in the text. Shown here are the stimulation sites in one subject. Brodmann cytoarchitectonic areas are superimposed onto the MRI image (original in color). MED, medial frontal stimulation site; LAT, lateral frontal stimulation site.

2.4. Event-related brain potentials (ERPs)

The electroencephalogram (EEG) was recorded from 29 scalp locations including all standard 10–20 system (Jasper, 1958) positions against the algebraic mean of the activity at the mastoid electrodes (bandpass 0.01–70 Hz, digitization rate 250 Hz) using tin electrodes mounted in an elastic cap. Vertical eye movements were monitored with an electrode below the right eye and horizontal eye movements were recorded with one electrode located in the outer canthus of the right eye. After artifact rejection for the eye and frontal channels, the EEG signal was averaged separately time-locked to the responses for each stimulus-response combination for epochs of 1024 ms including a 300 ms pre-response interval. The rejection criteria were obtained separately for each individual subject by interactive determination of the amplitude of a number of eye-blink artifacts and were set such that eye blinks would be picked up by the artifact rejection algorithm. Rejection rates were below 15% in all subjects and conditions. A low-pass filter (8 Hz) was applied in all the computations and averages reported.

In order to assess a possible temporal decline in the extent of the functional lesion induced by rTMS, each of the blocks was subdivided in two halves. In addition to ERPs across the entire block, separate averages were obtained for the first and second halves.

ERPs were quantified by mean amplitude measures within time-windows specified in the Section 3 relative to a –50 to 0 ms baseline at the sites with the maximum effects. These data were entered into analysis of variance (ANOVA) statistics with the Huynh-Feldt epsilon correction applied as necessary. Whenever effects of the factor stimulation condition were obtained, these were followed up by standard post hoc (Scheffé) comparisons.

3. Results

3.1. Behavioral performance

The mean reaction times for correct trials and error trials are shown separately for congruent and incongruent trials in Table 1 for the 3 different stimulation conditions. A highly significant main effect of response type ($F(1, 10) = 205$, $P < 0.0001$) was obtained. No main effect of stimulation condition was found for the reaction times ($F(2, 20) = 0.72$, not significant (n.s.)) and no interaction of response type \times stimulation condition was seen ($F(2, 20) = 0.58$, n.s.). There was no effect of congruency ($F(1, 10) = 0.47$, n.s.) and no interaction between response type and congruency ($F(1, 10) = 1.16$, n.s.). Additional analyses were carried out to assess, whether post-error slowing was present in the current experiment and whether it was differentially affected by the different stimulation conditions. No post-error slowing was found in the present experiment.

The correction times were determined as the time period between the first (erroneous) button press and the second (corrective) button press (Table 1). These were very fast, but no main effect of stimulation condition was seen ($F(2, 20) = 0.98$, n.s.).

While the percentage of errors (see Table 1 for means) did not differ between the different conditions ($F(2, 20) = 0.53$, n.s.), there was a significant difference in the percentage of corrected errors between the different stimulation conditions ($F(2, 20) = 3.59$, $P < 0.047$). Post hoc tests showed a difference between the ‘No TMS’ and ‘Medial TMS’ conditions ($P < 0.05$). None of the other comparisons were significant.

Table 1
Behavioral measures: group means (SD)

Measure	No TMS	Lateral TMS	Medial TMS
RT correct congruent	352 (17)	355 (18)	356 (18)
RT correct incongruent	352 (18)	354 (17)	358 (18)
RT incorrect congruent	301 (20)	299 (18)	306 (25)
RT incorrect incongruent	297 (15)	298 (15)	301 (21)
RT corrective response	189 (23)	196 (32)	188 (25)
% Errors	25.1 (6.2)	23.4 (5.3)	23.2 (3.8)
% Corrections	92.1 (3.1)	90.0 (3.7)	88.3 (4.5)

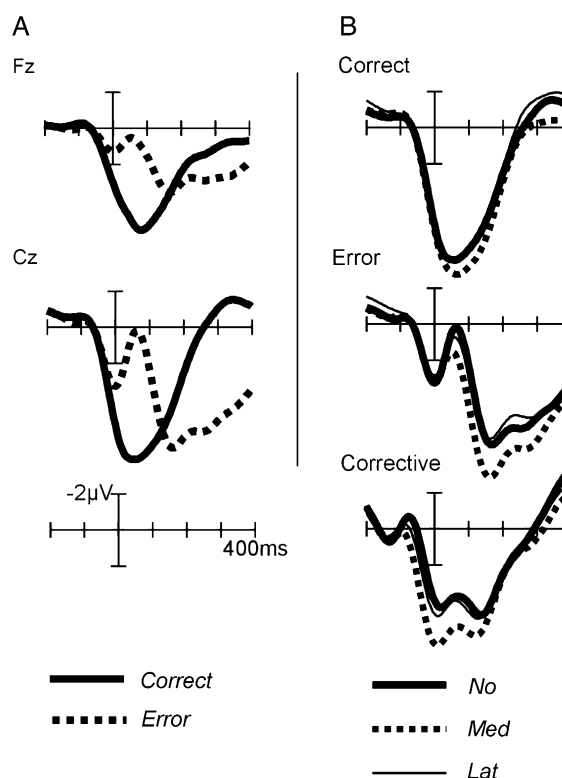


Fig. 2. (A) Response locked grand average ERPs for correct and incorrect responses in the ‘no stimulation’ condition. A clear ERN component emerges for the error trials. (B) Response locked grand average ERPs contrasting correct, error, and corrective responses from all 3 stimulation conditions for the Cz site. Medial frontal stimulation leads to a smaller ERN followed by a pronounced frontal positivity (Pe) in the error trials. Also, the ERPs to the corrective responses are characterized by a more positive going waveform.

3.2. Event-related potentials

Fig. 2A shows the ERPs time-locked to the correct and erroneous responses in the no-stimulation condition. The ERN component appeared immediately after the response for the error trials and was followed by the positive component or error-positivity (Pe; Falkenstein et al., 1991), i.e. from about 150 ms onwards the ERPs to the errors were more positive than those to the correct responses. To better allow comparison of the 3 conditions, the respective ERPs are overlaid in Fig. 2B. Here, a pronounced effect of condition emerged, with the ERN for the medial TMS condition being smaller. Statistically, this was reflected in a main effect of condition (mean amplitude 30–80 ms, Fz and Cz electrode, $F(2, 20) = 3.68$, $P < 0.05$). Post hoc comparisons revealed a significant difference between conditions ‘no TMS’ and ‘medial TMS’ ($P < 0.05$), while the comparison medial vs. lateral TMS showed a trend towards significance ($P = 0.09$).

The subsequent positivity (Pe) was quantified by a mean amplitude measure (150–350 ms) on 10 frontocentral channels (F3/4, Fc1/2, Fc5/6, Fz, Cz, Cp1/2), where the component was found to be maximal, with the channels

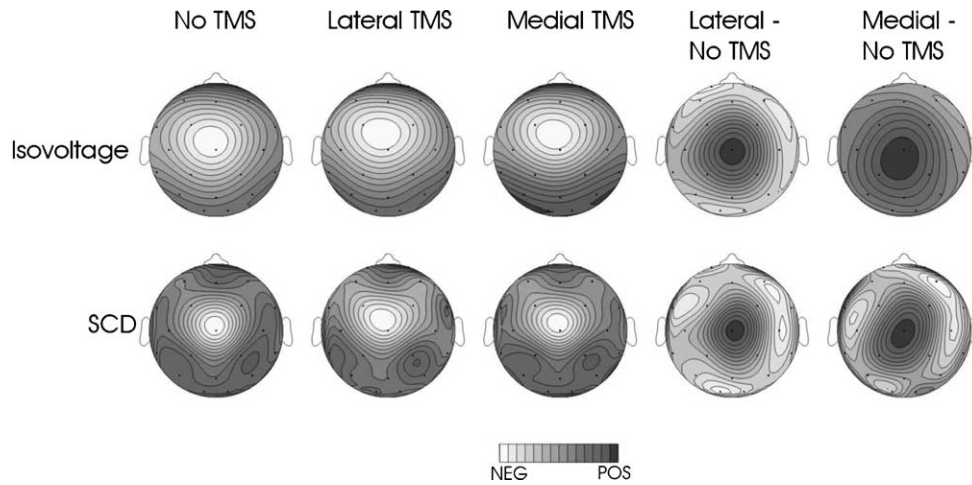


Fig. 3. Spline-interpolated isovoltage and source current density maps depicting the average voltage (30–80 ms) measured on bandpass filtered (1–8 Hz, half amplitude cutoff) response locked ERPs to error trials. The time window was centered upon the peak of the ERN in the bandpass-filtered waveforms.

entered as levels of a topography factors. A main effect of stimulation condition was obtained ($F(2, 20) = 9.90$, $P < 0.001$) reflecting the greater amplitude of the Pe in the medial TMS condition. The post hoc comparisons of ‘no TMS’ vs. ‘medial TMS,’ and ‘medial TMS’ vs. ‘lateral TMS’ were significant (both $P < 0.01$).

The scalp distribution of the ERN component is illustrated by spline interpolated isovoltage maps in Fig. 3. Rather than computing these distributions from error minus correct difference waves, they were obtained from bandpass-filtered (1–8 Hz, half amplitude cutoff) waveforms to the error trials. All 3 conditions show a similar distribution of the ERN.

Fig. 4 shows the ERPs obtained for the first and second halves of each 3 min block. No systematic differences are apparent upon visual inspection, which is corroborated by a series of statistical analyses that did not reveal any effects of halves.

The ERPs to corrective responses are shown in Fig. 2B. Again, the medial stimulation condition led to a more positive waveform compared to the other conditions (mean amplitude 0–100 ms, Fz, Cz, Fc1, Fc2 electrodes, $F(2, 20) = 9.91$, $P < 0.001$) with the post hoc tests showing the medial stimulation condition to have a more positive waveform than both, the ‘No TMS’ ($P < 0.01$) and the ‘lateral TMS’ ($P < 0.01$) conditions.

4. Discussion

The present investigation revealed reliable and anatomically selective effects of transcranial magnetic stimulation on behavior and event-related brain potentials related to error detection and correction. RTMS was applied to locations known to be involved in action monitoring from previous neuroimaging (Carter et al., 1998; Kiehl et al.,

2000; Menon et al., 2001; Ullsperger and von Cramon, 2001), electrophysiological (Dehaene et al., 1994; Miltner et al., 1998), and lesion studies (Gehring and Knight, 2000; Segalowitz et al., 2000; Stemmer et al., 2000; Swick and Turken, 2002; Ullsperger et al., 2002). To summarize, stimulation to a medial frontal site prior to the task revealed: (i) a reduced error correction rate, (ii) a reduction in the amplitude of the error-related negativity (ERN) and (iii) a positive shift in the 150–350 ms range in the response-locked ERPs to the errors as well as to the corrective responses. By contrast, stimulation of a right lateral site did not show an effect on the response-locked ERPs and the correction rate.

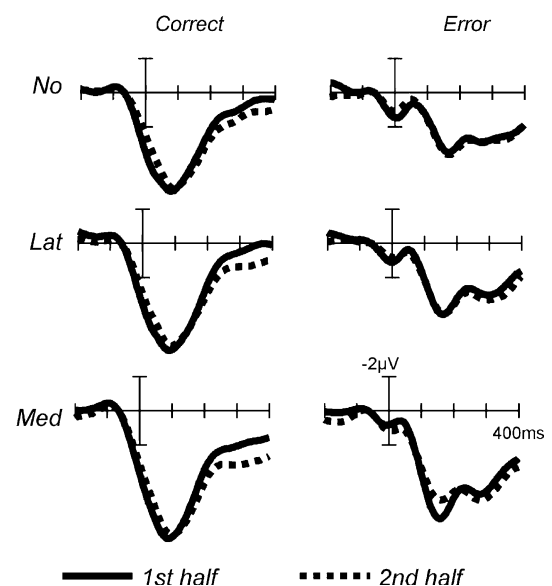


Fig. 4. When ERPs from the first and second half of each block are contrasted, no systematic effect was observed, indicating that stimulation effects are rather long-lived (data from Fz-site).

As discussed in Section 1, slow repetitive transcranial magnetic stimulation as used in the present experiment has been shown to induce an inhibitory effect outlasting the actual stimulation by at least several minutes (Chen et al., 1997; Maeda et al., 2000; Pascual-Leone et al., 1998; Rollnik et al., 2003). We will thus consider the effects observed in the current experiment as being due to a (relative) functional lesion of the brain areas stimulated. Neither a medial frontal nor a right lateral frontal functional lesion had an influence on the rate of errors in the present experiment indicating that the stimulation did not interfere with the perceptual processing of the stimuli and response preparation. The ERN, however, as an electrophysiological sign of error detection was found to be reduced by medial frontal stimulation as was the rate of corrective responses. This suggests that the error detection process and, subsequently, the corrective action is disturbed by medial stimulation to a certain degree. It has to be kept in mind that the stimulation was conducted prior to each experimental block in the ERP experiment. Therefore, only a mild disruption of the error detecting system might have occurred. Different studies have recently shown that medial frontal lesions including the ACC lead to a reduced or even absent ERN (Segalowitz et al., 2000; Stemmer et al., 2000; Swick and Turken, 2002). Previous experiments of our group (Rodriguez-Fornells et al., 2002) contrasting a condition, in which the subjects were encouraged to correct response errors (as in the present experiment), with a condition that prohibited correction, have revealed that the ERN occurs later than or, at the very least, in parallel to the preparation of a corrective motor response. This means, that the ERN, while reliably indexing error detection of the subject, is likely not the correlate of the internal error signal itself, which must precede the preparation of the corrective action. As in the present experiment both the ERN and the percentage of corrected errors were influenced by medial TMS, it appears that the error signal proper was altered in this stimulation condition.

Subsequent to the ERN component, the response-locked ERP in the medial stimulation condition also showed a significantly increased positivity. This may well be a modulation of the error positivity (Pe), which is thought to be independent of the ERN and believed to be associated with some later aspects of error processing or post-error processing such as conscious error monitoring, adjustment of response strategies or subjective/emotional assessment of the significance of an error (Davies et al., 2001; Falkenstein et al., 2000; Van Veen and Carter, 2002; Vidal et al., 2000). A recent study has proposed that the Pe component indexes the degree of awareness of an error (Nieuwenhuis et al., 2001). These authors used an antisaccade task which tend to induce numerous erroneous reflexive saccades, and asked their subjects to report whether they had made an erroneous eye movement or not. The ERN component was present for both, perceived and unperceived errors. By contrast, the Pe was only seen for the perceived saccadic errors. In a similar

fashion, Vidal et al. (2000) also found a dissociation between the ERN and the Pe component. In correct trials with electromyographic activity in the inappropriate response hand but no overt erroneous response (partial errors) they found a clear ERN but a reduced Pe, while for overt errors both components showed larger amplitudes. These authors also proposed that the Pe should be related to the degree of awareness of the errors. Following this interpretation, the increased positivity after medial rTMS would indicate that the subjects might have been more aware of their errors than in the other conditions. However, the finding that in the same condition subjects corrected a smaller percentage of their errors clearly goes against this interpretation.

Falkenstein et al. (2000) alternatively proposed that the Pe component might index the subjective or emotional significance of the error. Following this interpretation the medial rTMS stimulation might have increased the negative valence of the errors committed by our subjects. While we have no independent means to assess the emotional impact of the errors in the current study, this interpretation seems plausible considering the direct link of medial frontal cortex to emotional processing (Bush et al., 2000).

Interestingly, no effect of lateral frontal stimulation was observed on ERN amplitude or corrective responses. This is in line with previous observations in patients with unilateral lesions to the lateral frontal cortex (Gehring and Knight, 2000) who did not show a reduction of the ERN in error trials (but see Ullsperger et al., 2002). In patients with lateral prefrontal lesions, an ERN-like deflection for correct trials has been described previously, however. In the view of Cohen et al. (2000) the lateral prefrontal cortex supports the representation of task demands (e.g. what is the target?, what is the relevant stimulus dimension?). If this representation is damaged by a lateral prefrontal lesion, increased response conflicts are experienced by the ACC which in turn explains the ERN on correct trials. In the present investigation no ERN-like activity was found for correct trials, however, suggesting that either the current TMS stimulation protocol was not sufficient to impair task representations or to elicit a functional lesion in lateral PFC or that some additional factors were present the previously cited studies.

To summarize, the present study once again underscores the role of medial frontal structures in error detection and correction. Moreover, it points to the possibilities of the rTMS functional lesion approach in the investigation of the human error processing network.

Acknowledgements

This study was supported by DFG grant MU1311/11-1 awarded to T.F.M. A.R.F. also received support of the Spanish government. We thank Wido Nager, Andreas Niesel and Jobst Kilian for their help.

References

- Angel RW, Alston W, Higgins JR. Control of movement in Parkinson's disease. *Brain* 1970;93:1–14.
- Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. *Lancet* 1985;1:1106–7.
- Bernstein PS, Scheffers MK, Coles MG. 'Where did I go wrong?' A psychophysiological analysis of error detection. *J Exp Psychol Hum Percept Perform* 1995;21:1312–22.
- Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD. Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature* 1999;402:179–81.
- Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD. Conflict monitoring and cognitive control. *Psychol Rev* 2001;108:624–52.
- Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci* 2000;4:215–22.
- Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD. Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 1998;280:747–9.
- Carter CS, Botvinick MM, Cohen JD. The contribution of the anterior cingulate cortex to executive processes in cognition. *Rev Neurosci* 1999;10:49–57.
- Carter CS, Macdonald AM, Botvinick M, Ross LL, Stenger VA, Noll D, Cohen JD. Parsing executive processes. strategic vs. evaluative functions of the anterior cingulate cortex. *Proc Natl Acad Sci USA* 2000;97:1944–8.
- Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, Cohen LG. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology* 1997;48:1398–403.
- Christ S, Falkenstein M, Heuer H, Hohnsbein J. Different error types and error processing in spatial stimulus-response-compatibility tasks. Behavioural and electrophysiological data. *Biol Psychol* 2000;51:129–50.
- Cohen JD, Botvinick M, Carter CS. Anterior cingulate and prefrontal cortex: who's in control? *Nat Neurosci* 2000;3:421–3.
- Coles MG, Scheffers MK, Fournier L. Where did you go wrong? Errors, partial errors, and the nature of human information processing. *Acta Psychol (Amst)* 1995;90:129–44.
- Coles MG, Scheffers MK, Holroyd CB. Why is there an ERN/Ne on correct trials? Response representations, stimulus-related components, and the theory of error-processing. *Biol Psychol* 2001;56:173–89.
- Davies PL, Segalowitz SJ, Dywan J, Pailing PE. Error-negativity and positivity as they relate to other ERP indices of attentional control and stimulus processing. *Biol Psychol* 2001;56:191–206.
- Dehaene S, Posner MI, Tucker DM. Localization of a neural system for error detection and compensation. *Psychol Sci* 1994;5:303–5.
- Elton M, Band G, Falkenstein M. To err is human. *Biol Psychol* 2000;51:83–5.
- Eriksen BA, Eriksen CW. Effects of noise letters upon the identification of target letters in a non-search task. *Percept Psychophys* 1974;16:143–9.
- Falkenstein M, Hohnsbein J, Hoormann J, Blanke L. Effects of crossmodal divided attention on late ERP components. II. Error processing in choice reaction tasks. *Electroenceph clin Neurophysiol* 1991;78:447–55.
- Falkenstein M, Hohnsbein J, Hoormann J. Event-related potential correlates of errors in reaction tasks. *Electroenceph clin Neurophysiol Suppl* 1995;44:287–96.
- Falkenstein M, Hoormann J, Christ S, Hohnsbein J. ERP components on reaction errors and their functional significance. a tutorial. *Biol Psychol* 2000;51:87–107.
- Garavan H, Ross TJ, Murphy K, Roche RAP, Stein EA. Dissociable executive functions in the dynamic control of behavior: inhibition, error detection, and correction. *Neuroimage* 2002;17:1820–9.
- Gehring WJ, Fencsik DE. Functions of the medial frontal cortex in the processing of conflict and errors. *J Neurosci* 2001;21:9430–7.
- Gehring WJ, Knight RT. Prefrontal-cingulate interactions in action monitoring. *Nat Neurosci* 2000;3:516–20.
- Gehring WJ, Coles MG, Meyer DE, Donchin E. A brain potential manifestation of error-related processing. *Electroenceph clin Neurophysiol Suppl* 1995;44:261–72.
- George MS, Wassermann EM, Kimbrell TA, Little JT, Williams WE, Danielson AL, Greenberg BD, Hallett M, Post RM. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression. a placebo-controlled crossover trial. *Am J Psychiatry* 1997;154:1752–6.
- Gerloff C, Corwell B, Chen R, Hallett M, Cohen LG. Stimulation over the human supplementary motor area interferes with the organization of future elements in complex motor sequences. *Brain* 1997;120:1587–602.
- Hadland KA, Rushworth MFS, Passingham RE, Jahanshahi M, Rothwell JC. Interference with performance of a response selection task that has no working memory component: an rTMS comparison of the dorsolateral prefrontal and medial frontal cortex. *J Cogn Neurosci* 2001;13:1097–108.
- Holroyd CB, Coles MG. The neural basis of human error processing. reinforcement learning, dopamine, and the error-related negativity. *Psychol Rev* 2002;109:679–709.
- Holroyd CB, Dien J, Coles MG. Error-related scalp potentials elicited by hand and foot movements. evidence for an output-independent error-processing system in humans. *Neurosci Lett* 1998;242:65–8.
- Jahanshahi M, Rothwell JC. Transcranial magnetic stimulation studies of cognition: an emerging field. *Exp Brain Res* 2000;131:1–9.
- Jahanshahi M, Profice P, Brown RG, Ridding MC, Dirnberger G, Rothwell JC. The effects of transcranial magnetic stimulation over the dorsolateral prefrontal cortex on suppression of habitual counting during random number generation. *Brain* 1998;121:1533–44.
- Jasper HH. The ten-twenty system of the international federation. *Electroenceph clin Neurophysiol* 1958;10:371–5.
- Kiehl KA, Liddle PF, Hopfinger JB. Error processing and the rostral anterior cingulate. an event-related fMRI study. *Psychophysiology* 2000;37:216–23.
- Luu P, Tucker DM. Regulating action. alternating activation of midline frontal and motor cortical networks. *Clin Neurophysiol* 2001;112:1295–306.
- Luu P, Collins P, Tucker DM. Mood, personality, and self-monitoring. negative affect and emotionality in relation to frontal lobe mechanisms of error monitoring. *J Exp Psychol Gen* 2000a;129:43–60.
- Luu P, Flaisch T, Tucker DM. Medial frontal cortex in action monitoring. *J Neurosci* 2000b;20:464–9.
- MacDonald III AW, Cohen JD, Stenger VA, Carter CS. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science* 2000;288:1835–8.
- Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. *Clin Neurophysiol* 2000;111:800–5.
- Menon V, Adelman NE, White CD, Glover GH, Reiss AL. Error-related brain activation during a Go/NoGo response inhibition task. *Hum Brain Mapp* 2001;12:131–43.
- Miltner WHR, Braun C, Coles MGH. Event-related brain potentials following incorrect feedback in a time-estimation task. Evidence for a 'generic' neural system for error detection. *J Cogn Neurosci* 1998;9:787–97.
- Nieuwenhuis S, Ridderinkhof KR, Blom J, Band GP, Kok A. Error-related brain potentials are differentially related to awareness of response errors. Evidence from an antisaccade task. *Psychophysiology* 2001;38:752–60.
- Niki H, Watanabe M. Prefrontal and cingulate unit activity during timing behavior in the monkey. *Brain Res* 1979;171:213–24.
- Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Canete C, Catala MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. *J Clin Neurophysiol* 1998;15:333–43.

- Pascual-Leone A, Walsh V, Rothwell JC. Transcranial magnetic stimulation in cognitive neuroscience – virtual lesion, chronometry, and functional connectivity. *Curr Opin Neurobiol* 2000;10:232–7.
- Rabbitt PM. Error correction time without external error signals. *Nature* 1966a;212:438.
- Rabbitt PM. Errors and error correction in choice-response tasks. *J Exp Psychol* 1966b;71:264–72.
- Rabbitt PM. Three kinds of error-signalling responses in a serial choice task. *Q J Exp Psychol* 1968;20:179–88.
- Rabbitt PM, Phillips S. Error-detection and correction latencies as a function of S-R compatibility. *Q J Exp Psychol* 1967;19:37–42.
- Rodriguez-Fornells A, Kurzbuch AR, Munte TF. Time course of error detection and correction in humans. Neurophysiological evidence. *J Neurosci* 2002;22:9990–6.
- Rollnik JD, Schubert M, Albrecht J, Wohlfarth K, Dengler R. Effects of somatosensory input on central fatigue. A pilot study. *Clin Neurophysiol* 2000a;111:1843–6.
- Rollnik JD, Schubert M, Dengler R. Subthreshold prefrontal repetitive transcranial magnetic stimulation reduces motor cortex excitability. *Muscle Nerve* 2000b;23:112–4.
- Rollnik JD, Siggelkow S, Schubert M, Schneider U, Dengler R. Muscle vibration and prefrontal repetitive transcranial magnetic stimulation. *Muscle Nerve* 2001;24:112–5.
- Rollnik JD, Düsterhöft A, Däuper J, Kossev A, Dengler R. Decrease of middle cerebral artery blood flow velocity after low-frequency repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex. *Clin Neurophysiol* 2003;113:951–5.
- Scheffers MK, Coles MG. Performance monitoring in a confusing world. error-related brain activity, judgments of response accuracy, and types of errors. *J Exp Psychol Hum Percept Perform* 2000;26:141–51.
- Scheffers MK, Coles MG, Bernstein P, Gehring WJ, Donchin E. Event-related brain potentials and error-related processing. An analysis of incorrect responses to go and no-go stimuli. *Psychophysiology* 1996;33:42–53.
- Scheffers MK, Humphrey DG, Stanny RR, Kramer AF, Coles MG. Error-related processing during a period of extended wakefulness. *Psychophysiology* 1999;36:149–57.
- Segalowitz SJ, Davies PL, Pailing PE, Stemmer B. Error related ERP responses. Error detection or beyond? *Psychophysiology* 2000;37:S10.
- Steinmetz H, Furst G, Meyer BU. Craniocerebral topography within the international 10–20 system. *Electroenceph clin Neurophysiol* 1989;72:499–506.
- Stemmer B, Segalowitz SJ, Witzke W, Lacher S, Schonle PW. Do patients with damage to the anterior cingulate and adjacent regions produce an error-related negativity (ERN)? *Psychophysiology* 2000;37:S95.
- Swick D, Turken AU. Dissociation between conflict detection and error monitoring in the human anterior cingulate cortex. *Proc Natl Acad Sci USA* 2002;99:16354–9.
- Turken AU, Swick D. Response selection in the human anterior cingulate cortex. *Nat Neurosci* 1999;2:920–4.
- Ullsperger M, von Cramon DY. Subprocesses of performance monitoring. a dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *Neuroimage* 2001;14:1387–401.
- Ullsperger M, von Cramon DY, Müller NG. Interactions of focal cortical lesions with error processing. Evidence from event-related brain potentials. *Neuropsychology* 2002;16:548–61.
- Van Veen V, Carter CS. The timing of action-monitoring processes in the anterior cingulate cortex. *J Cogn Neurosci* 2002;15:593–602.
- Van Veen V, Cohen JD, Botvinick MM, Stenger VA, Carter CS. Anterior cingulate cortex, conflict monitoring, and levels of processing. *Neuroimage* 2001;14:1302–8.
- Vidal F, Hasbroucq T, Grapperon J, Bonnet M. Is the ‘error negativity’ specific to errors? *Biol Psychol* 2000;51:109–28.
- Walsh V, Cowey A. Transcranial magnetic stimulation and cognitive neuroscience. *Nat Rev Neurosci* 2000;1:73–9.