DOI 10.1007/s00702-004-0229-5
J Neural Transm (2005) 112: 955–967

Journal of Neural Transmission
Printed in Austria

Changes in negative symptoms and EEG in schizophrenic patients after repetitive Transcranial Magnetic Stimulation (rTMS): an open-label pilot study

M. Jandl[1,2], **R. Bittner**[1], **A. Sack**[1], **B. Weber**[1], **T. Günther**[1], **D. Pieschl**[1], **W.-P. Kaschka**[2], and **K. Maurer**[1]

[1] Division of Neurophysiology and Neuroimaging, Department of Psychiatry and Psychotherapy I, Johann Wolfgang Goethe-University, Frankfurt, and
[2] Department of Psychiatry I, University of Ulm, Germany

Received March 26, 2004; accepted August 23, 2004
Published online October 27, 2004;

Summary. The effects of repetitive transcranial magnetic stimulation (rTMS) on schizophrenic negative symptoms (NS) and EEG topography were investigated in this pilot study.

10 patients with predominant NS were treated with 10 Hz rTMS over the left dorsolateral prefrontal cortex for 5 days. For NS ratings, the Scale for the Assessment of Negative Symptoms (SANS) was used. Both ratings and EEG recordings were obtained pre- and post-rTMS. Electrical activity changes were computed by Low Resolution Brain Electromagnetic Tomography.

SANS showed an improvement after rTMS, from 49.0 (SD: 10.7) to 44.7 (SD: 11.8) (means). EEG frequency bands were changed fronto-temporally (right) and were mainly decreases in delta- and beta- and increases in alpha1-activity, as well as decreases in beta-activity in the temporal and parieto-occipital regions (left).

Although we are aware of the limitations of this study, we assume a slight improvement in NS. The EEG findings refer to a possible neurophysiologic correlate of their improvement after rTMS.

Keywords: Schizophrenia, negative symptoms, repetitive Transcranial Magnetic Stimulation, EEG topography, Low Resolution Brain Electromagnetic Tomography.

Introduction

Negative symptoms in schizophrenia affect the course of the disease and impair function more than do positive symptoms. Atypical neuroleptics have therapeutic effects on the negative symptoms which are much less pro-

nounced than on the positive symptoms. In view of the relatively higher drug resistance rate, a search for other methods of treatment seems to be justified.

Correlations between negative symptoms and disturbed executive functions and attentiveness point to the involvement of the prefrontal cortex in negative symptoms (Gold, 1995). Left prefrontal hypometabolism correlated with negative symptoms (Dolan et al., 1993). In addition, neuroimaging findings have been correlated with the hypofrontality model of negative symptoms (Weinberger, 1986), although the overall results are inconsistent. A better model of the pathophysiology of negative symptoms might be based on abnormal fronto-temporal interaction (Liddle, 1997).

Recent meta-analyses of up to 12 controlled trials, mostly with high frequency rTMS (i.e. the 10 to 20 Hz range) in patients with Major Depression Disorder found a modest beneficial effect of rTMS over the left DLPFC compared to sham stimulation (McNamara, 2001; Holtzheimer, 2001). In contrast, only a few studies have been performed to investigate the effects of rTMS on negative symptoms in schizophrenia (Klein, 1999; Nahas, 2000; Schreiber, 2002). Short-term amelioration of mood has been found, particularly in depressed and schizophrenic patients after low frequency rTMS over the left and right DLPFC (Geller, 1995). Global improvement associated with an improvement of cerebral perfusion was found after right prefrontal 10 Hz rTMS (Schreiber, 2002), whereas slow right prefrontal stimulation did not affect negative symptoms (Klein, 1999). Though therapeutic effects seem inconsistent or transient (Nahas, 2000), we hypothesize that negative symptoms, i.e. affective and executive functions, could be improved by rTMS over left DLPFC (Moser, 2002). Our stimulation protocol was designed rather conservatively and is therefore more readily comparable to previous trials on this topic (Klein, 1999; Nahas, 2000; Schreiber, 2002), than oriented towards recent rTMS trials on depression.

Findings from studies on quantitative EEG in schizophrenia suggest that patients with predominant negative or positive symptoms have different neurophysiological profiles, supporting the hypothesis of hypofrontality (Gerez, 1995). Low EEG activity, i.e. the delta- and theta-power over temporal (Gattaz, 1992) or frontal (Begic, 2000; Winterer, 2000; Sponheim, 2000; Knott, 2001) regions, was found to be significantly increased in schizophrenia and particularly correlated with negative symptoms. This could be regarded as a marker that could differentiate between ''positive'' and ''negative'' schizophrenia (Begic, 2000). Somewhat less frequently, a decrease in alpha-power has also been found (Merrin, 1992; Merrin, 1996; Knott, 2001). Antipsychotic treatment both decreased delta and theta EEG activity and increased beta activity in patients with negative symptoms (Saletu, 1994) or obliterated the negative correlation between negative symptoms and alpha power (Merrin, 1992).

There have been only a few investigations on the effects of rTMS on EEG activity (Boutros, 2000, 2001; Loo, 2001; Graf, 2001); none of these examined patients with negative symptoms. It could be shown that rTMS increases the cortical activity, i.e. the peak frequency and the absolute power across scalp in normal subjects over a period of minutes after stimulation (Okamura, 2001). Laterality effects could also be found: application of low frequency rTMS over the right DLPFC, unlike sham stimulation, was accompanied by an increase in

theta activity contralaterally, associated with a reduction in anxiety ratings (Schutter, 2001).

In this open pilot study, we have aimed to assess the effects of high frequency rTMS over the left DLPFC in schizophrenic patients with predominant negative symptoms on the psychopathological ratings of these symptoms. We also assume that rTMS under these conditions will lead to altered activities of the different frequency bands in topographical EEG. On the basis of the cited previous studies on EEG activity in negative symptoms, we assume both local effects as well as effects in remote cortical regions. We hypothesize a decrease in low frequency bands in anterior regions, together with an improvement in negative symptoms. In this respect, the whole cortical volume will be examined using Low Resolution Brain Electromagnetic Tomography (LORETA) (Pascual-Marqui, 1994).

Material and methods

10 patients, 5 male, 5 female, all right-handed according to the Edinburgh Inventory (Oldfield, 1971), aged between 26 and 66 years ($M = 42.7$; $SD = 14.0$), mean duration of illness 18.1 years ($SD = 13.4$) with diagnosed schizophrenia according to DSM-IV criteria (American Psychiatric Association, 1994), were included in an open pilot study after their written informed consent had been given. The protocol was approved by the Ethic Committee of the Johann Wolfgang Goethe University Hospital in accordance with the 1964 Declaration of Helsinki of the World Medical Association, last amended in Edinburgh in 2000. All patients were carefully screened for their psychiatric and medical history and physically examined. Cranial Computed Tomography (CCT) or Magnetic Resonance Imaging (MRI) was carried out if not performed previously, with the aim of excluding structural cerebral alterations; no patient exhibited atrophic cerebral changes. We did not assess the coil – cortex distance. Provided that there is no atrophy, the DLPFC should be within the affected volume, with a depth of 2–3 cm (Bohning, 2000). Recent trials have found no correlation between coil – prefrontal cortex distance and antidepressant response (Kozel et al., 2000; Jorge et al., 2004), unlike coil – motor cortex distance and motoric threshold. Comorbidity of other psychiatric or neurological disorders, pacemaker, history of head surgery or cerebral seizures or hints of increased electrical excitability in resting EEG (assessed by a certified electroencephalographer) were reasons for exclusion. Dosages of classical ($n = 6$) and/or atypical antipsychotics ($n = 7$) and/or antidepressants ($n = 4$) were kept unchanged during a 4 week pre-study period, as well as during the study itself. Patients were recruited consecutively from the psychiatric wards and from the outpatient clinic. Clinically, positive symptoms were not dominant. Patients were suffering more from the negative symptoms. Except for the hallucination subscale, all positive symptoms subscales of the Brief Psychiatric Rating Scale (BPRS) (CIPS, 1986; Overall, 1972) showed not more than moderate scores (4) before rTMS.

Ratings were carried out at day 1 (pre-rTMS) and day 5 (post-rTMS): Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989), Hamilton Depression Scale (HAMD) (CIPS, 1986; Hamilton, 1960), Brief Psychiatric Rating Scale (BPRS), Scale for Extrapyramidal Side Effects (SEPS) (Simpson, 1970) as well as an eight point Clinical Global Impression (CGI) Severity Scale.

For the assessment of negative symptoms, the SANS was used and this is the primary outcome measure. For the assessment of affective changes, the HAMD was used. To register effects on general psychopathology, BPRS was used. Extrapyramidal symptoms (EPS) which could interfere with the assessment of negative symptoms should be ruled out by the SEPS.

15 min EEG recordings were obtained both directly before the first stimulation (day 1) and directly after the last stimulation (day 5). Patients were seated in a comfortable chair in a half supine position within a sound and light attenuated examination room. All subjects were instructed at all times in the same way to close their eyes during EEG acquisition.

Acquisitions and recordings of the EEG signals were carried out using a Neuroscan system (SynAmps 32 channel amplifier, headbox, PC and Neuroscan software, Neuroscan Inc., El Paso,

TX, USA). 26 Ag/AgCl scalp electrodes were positioned according to an extended ten-twenty system (Jasper, 1958; American Encephalographic Society, 1991) at Fp1, Fp2, F7, F8, F3, F4, FT9, FT10, Fz, T7, T8, C3, C4, CP5, CP6, Pz, P3, P4, TP9, TP10, P7, P8, P9, P10, O1, O2, referenced to Cz. For artefact identification, horizontal and vertical electro-oculograms (EOG) as well as a 1-channel ECG were recorded. Electrode impedance was kept below 5 kOhm. High pass cut off was set at 0.53 Hz, low pass cut off at 70 Hz, no notch filter, digitization rate was 500 Hz. Previous work could proof the reliability of quantitative EEG data for the different frequency bands and scalp derivations over months (Pollock et al., 1991). Reliability was found sufficient to allow group comparisons rather than just individual comparisons (Burgess and Gruzelier, 1993).

RTMS was administered to the patients on 5 successive days between 9 and 11 a.m. using a Medtronic stimulator with circular coil (MagPro, MC-125, $r = 6$ cm, Medtronic GmbH, Düsseldorf, Germany) over the left DLPFC. The center of the anterior part of the coil (not the center of the coil), facing the handle, was positioned over the left DLPFC, 5 cm (along and adjacent to the surface of the scalp) anterior the site over the motor cortex, where the motor threshold (MT) was determined. So the handle of the coil pointed in direction of (the site of) the motor cortex (where MT was determined) but was tilted away from the head by more than 2 cm, due to the tight contact with the scalp surface of the anterior part of the coil and the curve of the skull. MT was defined by the reproducible acquisition of 5 out of 10 motoric evoked potentials (MEP) of the right m. abd. poll. brev., displayed in a Jaeger Toennies Multiliner system (VIASYS Healthcare GmbH, Höchberg, Germany). During MT assessment, patients were asked to relax their hands. Stimulation strength was 100% of the strength at MT; the safety guidelines of the International Society of Transcranial Stimulation (Wassermann, 1998) were observed. Stimulation frequency was 10 Hz, 20 trains, 3.5 s duration per train, inter train interval (ITI) 10 s, number of stimuli per session 700.

EEG data were processed off-line by the Analyzer Software (Brain Products GmbH, Munich, Germany). Raw data were filtered, high pass 0.53 Hz, low pass 30 Hz, each 12 dB/oct slope. The continuous EEG data were segmented to 2 s epochs. After applying a semiautomatic artefact rejection program with visual examination of all segments by an experienced electroencephalographer, 25 epochs of each patient were kept. A new data set was created for each epoch, so from 10 patients data sets were available from 25 epochs per session, each before and after 5 days rTMS.

To compute the distribution of the current sources over the whole cortical volume from the scalp surface potentials, we used LORETA (Pascual-Marqui, 1994, 1999). Its solution of the ''inverse problem'' is based on the assumption that neighboring neurons show the highest amount of synchronized electrical activity and that the smoothest three-dimensional distribution of intracranial electrical activity is selected out of an infinite number. The three-shell spherical head model of this is fitted to the head geometry of the Talairach atlas of the human brain (Talairach, 1997).

Using Fourier transformation, the EEG epochs were filtered to the frequency bands: delta (1.5–6 Hz), theta (6.5–8 Hz), alpha1 (8.5–10 Hz), alpha2 (10.5–12 Hz), beta1 (12.5–18 Hz), beta2 (18.5–21 Hz) and beta3 (21.5–30 Hz) (Kubicki, 1979), producing data sets of all frequency bands of each patient and each session, based on EEG power (i.e. squared amplitude).

The mean baseline and follow up rating scale values were compared using a paired t-test for dependent samples.

For pairwise statistical comparison of the log-transformed EEG power-maps of each frequency band, the paired t-test was carried out. Critical t-values of $p < 0.05$ were calculated by 5000 randomizations (Holmes, 1996). The t-test was performed on a voxel by voxel basis between pre-rTMS- and post-rTMS-maps. To visualize the three-dimensional cortical locations of the differences after 5 days rTMS, the distribution of the clusters of positive and negative t-values were displayed for each frequency band.

Results

All patients completed the protocol. No severe side effects were observed.

Primary outcome measure: SANS-score decreased significantly during rTMS from $M = 49.0$; $SD = 10.7$ at day 1 (baseline) to $M = 44.7$; $SD = 11.8$ at day 5 (follow up); $t = 4.872$; $p < 0.001$ (Fig. 1).

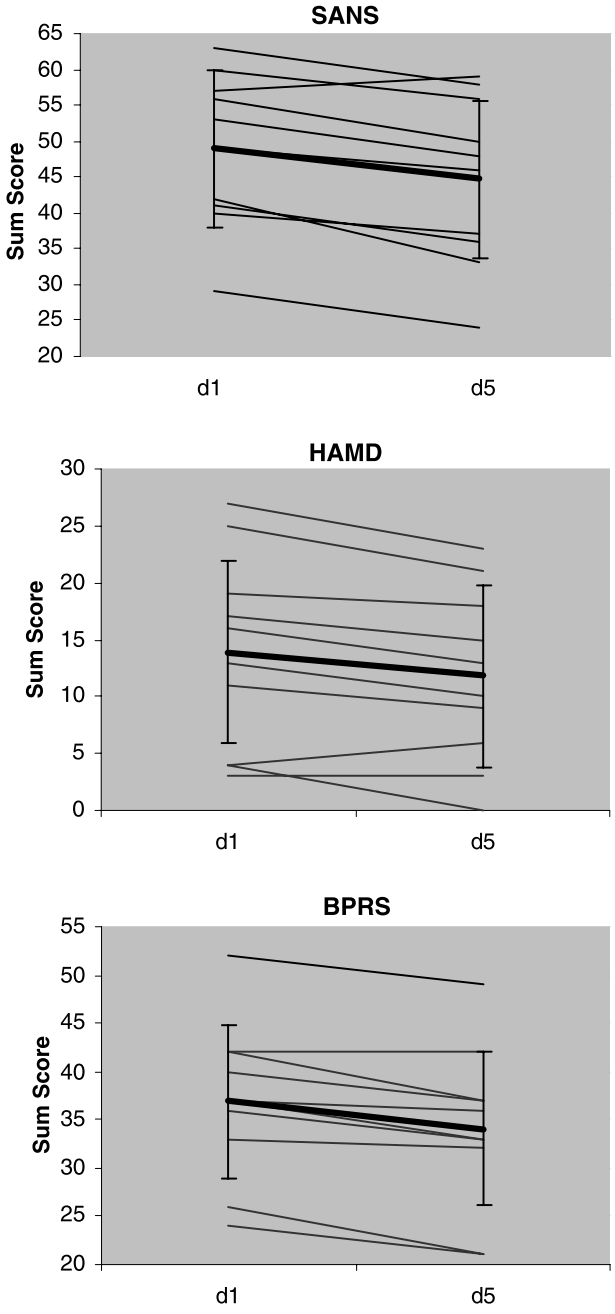

Fig. 1. Rating scales with sum scores of each patient at day 1 (before) and day 5 (after rTMS). *SANS* Scale for the Assessment of Negative Symptoms, *HAMD* Hamilton Depression Scale, *BPRS* Brief Psychiatric Rating Scale

Secondary outcome measures: HAMD-score decreased significantly from $M = 13.9$; $SD = 8.6$ at day 1 (baseline) to $M = 11.8$; $SD = 7.6$ at day 5 (follow up); $t = 3.372$; $p < 0.01$. While changes in scores below 8 were inconsistent, all

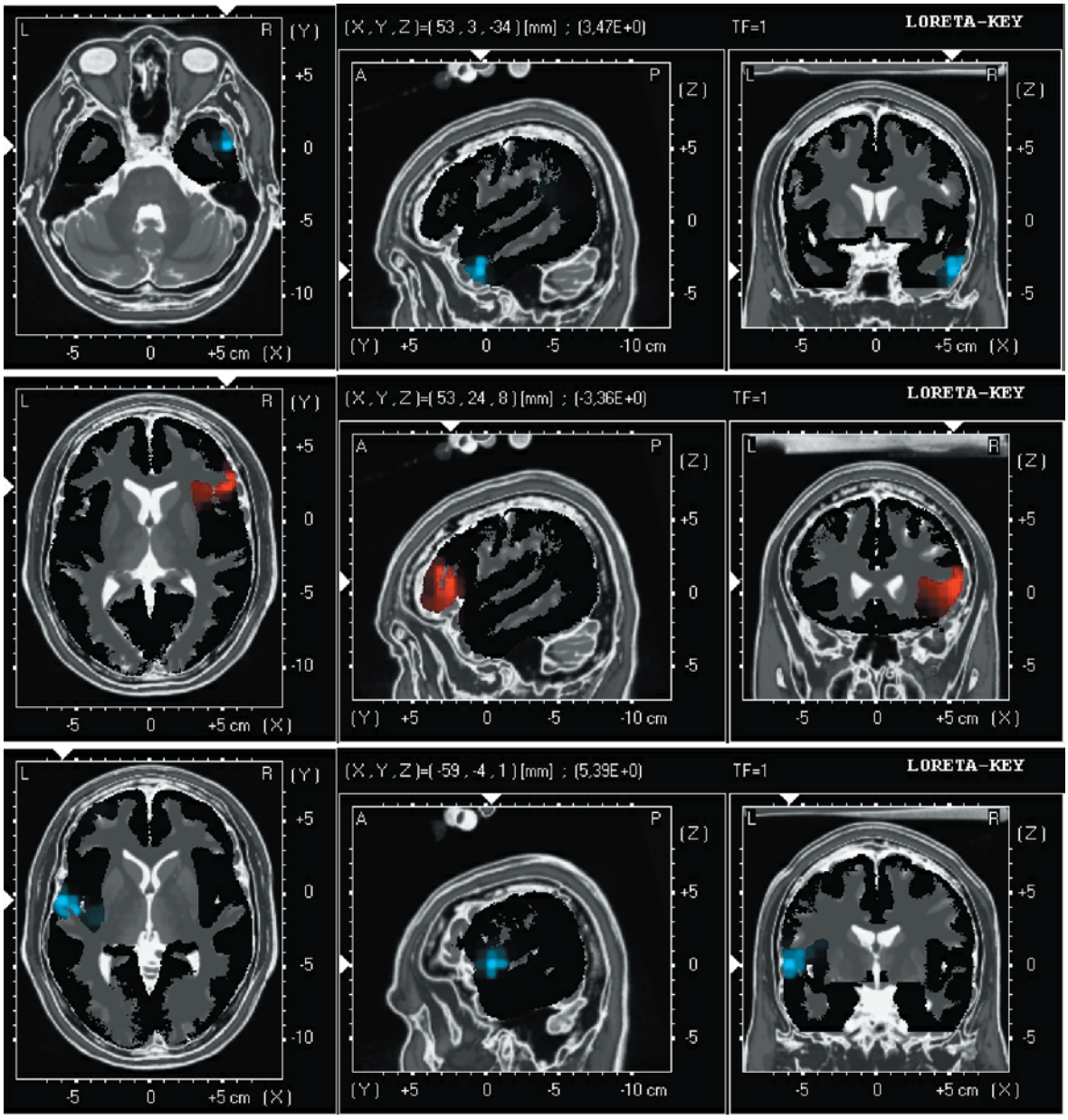

Fig. 2. Low Resolution Brain Electromagnetic Tomography (LORETA) views of the voxelclusters with extreme t-values of the delta-, alpha1- and beta2-frequency band T-values (each on top right, central views, in parentheses); transversal, saggittal and coronal slices (from left to right) with Talairach coordinates (X, Y, Z in mm) of the delta-, alpha1- and beta2-frequency band (from top to bottom). Regions with significant decrease of power after rTMS are displayed in blue; regions with a significant increase are displayed in red. For clarification a non-linear representation of color intensity is chosen

Table 1. Significantly changed EEG power locations of the respective frequency bands. Frequency bands, extreme t-values in descending standing, corresponding Talairach-coordinates, hemisphere (*R* right, *L* left), nearest BA (= Brodmann-Area) and description of brain region (*GTM* Gyrus temporalis medialis, *GTS* Gyrus temporalis superior, *GpostC* Gyrus postcentralis, *GFM* Gyrus frontalis medialis, *GFS* Gyrus frontalis superior, *GFI* Gyrus frontalis inferior, *LPI* Lobulus parietalis inferior, *GC* Gyrus cinguli, *GpraeC* Gyrus praecentralis, *LPS* Lobulus parietalis superior, *TL* Temporal Lobe, *PL* Parietal Lobe, *FL* Frontal Lobe, *LL* Limbic System, *OL* Occipital Lobe). Number of significantly changed power locations of the respective frequency bands (if >10 only those ten with the most extreme t-values are listed)

Frequency band	t-value	Talairach-coordinates			Hemisphere	BA	Brain region	Number of significantly changed locations
		X	Y	Z				
Delta (1.5–6 Hz)	3.46	53	3	−34	R	21	GTM, TL	
	2.98	53	−39	22	R	13	GTS, TL	
	2.34	60	−25	50	R	3	GpostC, PL	
	2.34	53	−25	43	R	2	GpostC, PL	
	2.34	60	−32	50	R	40	GpostC, PL	
	2.09	25	−4	57	R	6	GFM, FL	
	2.09	25	3	50	R	6	GFM, FL	
	2.09	32	−4	64	R	6	GFM, FL	
	2.09	32	−4	50	R	6	GFM, FL	
	2.09	25	3	64	R	6	GFS, FL	
	...		...		...	...	...	21
Theta (6.5–8 Hz)	2.56	18	59	−20	R	11	GFS, FL	
	2.51	53	10	−34	R	21	GTM, TL	2
Alpha1 (8.5–10 Hz)	−3.36	53	24	8	R	45	GFI, FL	
	−3.10	46	17	−20	R	38	GTS, TL	
	−2.06	60	−32	1	R	21	GTM, TL	
	−2.06	46	−32	1	R	21	GTM, TL	
	−2.06	67	−39	1	R	22	GTM, TL	
	−2.06	60	−39	1	R	21	GTM, TL	6
Alpha2 (10.5–12 Hz)	–		–		–	–	–	0
Beta1 (12.5–18 Hz)	4.19	−38	−11	−6	L	21	Subgyral, TL	
	3.86	−52	−4	1	L	22	GTS, TL	
	2.89	−24	38	−13	L	11	GFM, FL	
	2.89	−24	45	−13	L	11	GFM, FL	
	2.47	11	−4	71	R	6	GFS, FL	
	2.47	25	10	−41	R	38	GTS, TL	
	2.47	25	10	−34	R	38	GTS, TL	
	2.42	−45	−39	57	L	40	GPI, PL	
	2.42	−45	−46	57	L	40	GPI, PL	
	2.42	−38	−39	57	L	40	GPI, PL	
	...		...		...	...	...	22
Beta2 (18.5–21 Hz)	5.39	−59	−4	1	L	22	GTS, TL	
	4.33	−38	59	−13	L	11	GFM, FL	
	4.33	−31	59	−13	L	11	GFS, FL	
	2.88	−31	17	−6	L	13	Insula, FL	
	2.88	−31	24	1	L	47	GFI, FL	
	2.80	−52	−53	50	L	40	LPI, PL	
	2.80	−45	−46	43	L	40	LPI, PL	
	2.80	−45	−46	50	L	40	LPI, PL	
	2.80	−52	−46	50	L	40	LPI, PL	
	2.59	−3	−4	29	L	24	GC, LL	
	...		...		...	...	...	46
Beta3 (21.5–30 Hz)	4.63	−66	−18	1	L	22	GTS, TL	
	4.54	−59	−4	22	L	4	GpraeC, FL	
	3.21	−31	−46	64	L	7	LPS, PL	
	3.20	−38	−32	57	L	40	GpostC, PL	
	2.82	−45	45	−6	L	47	GFM, FL	
	2.76	−38	−81	−13	L	18	OL	
	2.76	−45	−81	−13	L	18	OL	
	2.74	−52	−67	−6	L	19	OL	
	2.16	−24	−11	71	L	6	GpraeC, FL	
	2.16	−24	−11	64	L	6	GpraeC, FL	
	...		...		...	...	...	16

scores above 8 decreased after rTMS. BPRS-score significantly decreased from $M = 36.9$; $SD = 8.1$ at day 1 to $M = 34.1$; $SD = 8.5$ at day 5; $t = 5.250$; $p < 0.001$ (Fig. 1).

Additional measure: SEPS-score did not change, $M = 2.40$; $SD = 1.84$ at day 1 and $M = 1.90$; $SD = 1.67$ at day 5.

Clinical Global Impression (CGI) Severity Scale: All patients showed a changing score after rTMS between 4, ''only little improved'' and 2, ''very much improved'' with an effectiveness index between 4, ''slight'' and 2, ''extensive''.

The analysis of the EEG frequency bands revealed changes after rTMS. Significantly decreased power of the delta-, theta-, beta1-, beta2- and beta3-frequency bands, significantly increased power of the alpha1-band; only the alpha2-band was unchanged.

The highest excesses in differences of the delta-, theta- and alpha-bands were found on the right side, those of the three beta-bands on the left side.

All significant changes in the frequency bands were only found in one direction (i.e. only significant positive or negative changes all over the whole brain volume).

Using LORETA, the statistically most pronounced changes in the single frequency bands can be topographically assigned to the following cortical generator locations: the clearest decrease in delta power after rTMS best matched the right medial temporal gyrus (GTM), Brodmann Area (BA) 21, according to the Talairach coordinates. The clearest decrease in the theta band best matched the right superior frontal gyrus (GFS) (BA 11). The highest increase in alpha1 power after rTMS best matched the right inferior frontal gyrus (GFI) (BA 45). All three beta bands showed decreased frequency power after rTMS, beta1 being most pronounced in the left temporal, subgyral region (BA 21), and beta2 and beta3 in the left superior temporal gyrus (GTS) (BA 22) (Fig. 2). On closer examination of the voxel clusters with lower (than the above mentioned) changes after rTMS, the most frequent changes were those in the beta2-band, followed by the beta1-, delta-, beta3-, alpha1 and theta-bands (Table 1).

If the analysis is performed with larger cerebral regions: right (pre)frontal: decreases in theta- and full beta-power together with an increase in alpha-power; left temporal: decreases in delta- and theta-power together with an increase in alpha-power and a decrease in full beta-power; right cingulum: decrease in delta-power. Decreases in full beta-power were also found in the left parietal, occipital and parahippocampal cortices.

Discussion

In view of the fact that there have been only very few trials on the effects of rTMS in negative symptoms of schizophrenia, it seemed justified to plan this trial as an open pilot study. We are also aware of its further limitations: no placebo control, the small sample size, the concomitant medication and the short duration of treatment, respectively. Our small sample size is also quite comparable with previous trials on schizophrenic patients with samples of up to 15 patients (Klein, 1999); even meta-analyses on depression listed sample sizes

of only between 3 and 35 patients per group (McNamara, 2001; Martin, 2003). The problem of concomitant medication is also evident. Most of the previous rTMS studies on schizophrenic as well as on depressive patients were add-on studies (see also the meta-analyses of McNamara and Martin).

During the course of the trial, negative symptoms improved, as expressed by a slight but significant decrease in the SANS-score. An improvement in depressive symptoms could also be shown by a slightly decreased HAMD-score. It seems there was a floor effect. The decrease was due to the patients with at least mild depressive symptoms. General psychopathology, assessed by the BPRS, improved slightly but significantly in the course of the trial. EPS, controlled by the SEPS, remained unchanged, so there is no relevant interference with the assessment of negative symptoms. Though the general differences in the scores were low, clinical changes could be noticed in the social environment of the patients (relatives and ward personnel), which corresponds with the CGI changes after rTMS between ''only little improved'' and ''very much improved''. Because of the limitations in the study design, our data should be interpreted with care, although indications of positive effects on negative symptoms in schizophrenia after rTMS over the left DLPFC could be seen, other interpretations, such as care- or placebo-effects, are conceivable.

It was another objective of the trial to examine the effects of higher frequency rTMS over the left DLPFC on EEG topography. After 5 days rTMS, hemispherical, regional and frequency-related changes in EEG activity could be seen: Most changes were found right (pre)frontal (BA 6, GFM, GFS, and GFI), being mainly decreases in the activity of delta- and beta-frequencies, as well as increases in alpha1-frequency. (Compared with the other frequency bands, decreases in theta-band activity were rare; no significant changes were shown in the alpha2-band.) Apart from that, the clearest delta-band decreases were found in the right temporal region.

If one assumes that lower EEG frequencies are associated with inhibitory brain functions, high frequency rTMS over the left DLPFC would have a disinhibitory contralateral effect, especially prefrontally and temporally. In addition, in the right prefrontal and right temporal regions, and nearly at the same location as the delta decrease, it led to an increase in middle frequency regions (alpha1), which are the frequency regions of relaxed resting conditions. Ipsilaterally, the left side was dominated by the decrease in beta-band activities, the most pronounced effects being left temporal (GTS), parahippocampal, parietal (GPI) and occipital. Because of that, high frequency rTMS would have an inhibitory effect on beta activity (which is associated with excitation), with a temporo-parietal focus. Our results too are quite inconsistent with the simplistic assumption supported in the literature (Grafman, 2000), whereby there is a relationship between fast rTMS and excitatory effects and low rTMS and inhibitory effects, respectively, since we found both inhibitory and excitatory effects after high frequent rTMS. Also recent data are not in agreement with this oversimplification (Fitzgerald, 2002).

Thus our results on the effects of rTMS on the lower- and middle-frequency EEG-activities would be in accord with previous findings that increased delta-

and theta-power and decreased alpha-power in fronto-temporal regions are positively correlated with negative symptoms in schizophrenia (Begic, 2000; Winterer, 2000; Sponheim, 2000; Knott, 2001; Merrin, 1992, 1996). This would then be an indication of the neurophysiologic correlate which underlies the improvement in negative symptoms after rTMS.

Another more general explanation of the effects of rTMS is provided by the concept of an improvement in functional discoordinated brain states. This was first suggested by Pascual-Marqui (1999), who found an excess of these activities in schizophrenics compared to normal controls and concluded that there was inadequate information processing. Inhibitory as well as excitatory brain activity, are both decreased in resting EEG in favour of alpha activity. The slightly antidepressive effect of higher frequency rTMS over the left DLPFC that we found is not so easily interpreted, particularly as we did not find any significant changes in brain activity at that location. It could be important to differentiate between short term effects right after rTMS, within a time frame of seconds up to a few minutes (Ilmoniemi et al., 1997; Chen et al., 2003) and effects following rTMS after hours or days. The former were found at the site of stimulation, but more general effects were also found (Okamura et al., 2001). In contrast, it is known that only contralateral effects on EEG are maintained for up to more than one hour after stimulation (Schutter et al., 2001). It is still unclear if the existence of local or remote effects depends on the stimulation intensity used, as cause-effect relationships are still somewhat speculative. However, there is probable involvement of other brain regions, especially contralateral and also limbic regions.

Although they were in accord with the hypofrontality model of negative symptoms in schizophrenia, our EEG findings after rTMS should not be overinterpreted, as the clinical results cannot exclude placebo effects in this uncontrolled pilot study. Both EEG findings and clinical results should be replicated by a sham-controlled trial with a larger sample of untreated first episode-patients.

Acknowledgements

The authors would like to thank Dr. T. Koenig and Prof. T. Dierks (both Department of Psychiatry, University of Berne) for their kind support.

References

American Encephalographic Society (1991) Guidelines for standard electrode position nomenclature. J Clin Neurophysiol 8: 200–222

American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders, 4th edn. American Psychiatric Association, Washington DC

Andreasen NC (1989) The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations. Br J Psychiatry (Suppl 7): 49–58

Begic D, Hotujac L, Jokic-Begic N (2000) Quantitative EEG in ''positive'' and ''negative'' schizophrenia. Acta Psychiatr Scand 101: 307–311

Bohning DE (2000) Introduction and overview of TMS physics. In: George MS, Belmaker RH (eds) Transcranial magnetic stimulation in psychiatry. American Psychiatric Press, Washington, pp 13–44

Boutros NN, Berman RM, Hoffman RE, Miano AP, Campbell D, Ilmoniemi R (2000) Electroencephalogram and repetitive transcranial magnetic stimulation. Depress Anxiety 12: 166–169

Boutros NN, Miano AP, Hoffman RE, Berman RM (2001) EEG monitoring in depressed patients undergoing repetitive transcranial magnetic stimulation. J Neuropsychiatry Clin Neurosci 13: 197–205

Burgess AP, Gruzelier J (1993) Individual reliability of amplitude distribution in topographical mapping of EEG. Electroencephalogr Clin Neurophysiol 86(4): 219–223

Chen WH, Mima T, Siebner HR, Oga T, Hara H, Satow T, Begum T, Nagamine T, Shibasaki H (2003) Low-frequency rTMS over lateral premotor cortex induces lasting changes in regional activation and functional coupling of cortical motor areas. Clin Neurophysiol 114(9): 1628–1637

Collegium Internationale Psychiatriae Scalarum (CIPS) (1996) Internationale Skalen für Psychiatrie, 4th edn. Beltz, Göttingen

Dolan RJ, Bench CJ, Liddle PF (1993) Dorsolateral prefrontal cortex dysfunction in the major psychosis: symptoms or disease specificity? J Neurol Neurosurg Psychiatry 63: 468–473

Fitzgerald PB, Brown TL, Daskalakis ZJ, Chen R, Kulkarni J (2002) Intensity-dependent effects of 1 Hz rTMS on human corticospinal excitability. Clin Neurophysiol 113(7): 1136–1141

Gattaz WF, Mayer S, Ziegler P, Platz M, Gasser T (1992) Hypofrontality on topographic EEG in schizophrenia. Correlations with neuropsychological and psychopathological parameters. Eur Arch Psychiatry Clin Neurosci 241: 328–332

Geller V, Grisaru N, Abardanel JM (1997) Slow magnetic stimulation of prefrontal cortex in depression and schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 21: 105–110

Gerez M, Tello A (1995) Selected quantitative EEG (QEEG) and event-related potential (ERP) variables as discriminators for positive and negative schizophrenia. Biol Psychiatry 38(1): 34–49

Gold JM, Weinberger DR (1995) Cognitive deficits and the neurobiology of schizophrenia. Curr Opin Neurobiol 5: 225–230

Graf T, Engeler J, Achermann P, Mosimann UP, Noss R, Fisch HU, Schlaepfer TE (2001) High frequency repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral cortex: EEG topography during waking and subsequent sleep. Psychiatry Res 107: 1–9

Grafman J (2000) TMS as a primary brain mapping tool. In: George MS, Belmaker RH (eds) Transcranial magnetic stimulation in neuropsychiatry. American Psychiatric Press, Washington, pp 115–140

Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 12: 56–62

Holmes AP, Blair RC, Watson JD, Ford I (1996) Nonparametric analysis of statistic images from functional mapping experiments. J Cereb Blood Flow Metab 16: 7–22

Holtzheimer PE 3rd, Russo J, Avery DH (2001) A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. Psychopharmacol Bull 35: 149–169

Ilmoniemi RJ, Virtanen J, Ruohonen J, Karhu J, Aronen HJ, Naatanen R, Katila T (1997) Neural response to magnetic stimulation reveals cortical reactivity and connectivity. Neuroreport 8: 3537–3540

Jasper HH (1958) The ten twenty electrode system of the International Federation. Electroencephalogr Clin Neurophysiol 10: 371–375

Jorge RE, Robinson RG, Tateno A, Narushima K, Acion L, Moser D, Arndt S, Chemerinski E (2004) Repetitive transcranial magnetic stimulation as treatment of poststroke depression: a preliminary study. Biol Psychiatry 55(4): 398–405

Klein E, Kolsky Y, Puyerovsky M, Koren D, Chistyakov A, Feinsod M (1999) Right prefrontal slow repetitive transcranial magnetic stimulation in schizophrenia: a double-blind sham-controlled pilot study. Biol Psychiatry 46(10): 1451–1454

Knott V, Labelle A, Jones B, Mahoney C (2001) Quantitative EEG in schizophrenia and in response to acute and chronic clozapine treatment. Schizophr Res 50: 41–53

Kozel FA, Nahas Z, deBrux C, Molloy M, Lorberbaum JP, Bohning D, Risch SC, George MS (2000) How coil-cortex distance relates to age, motor threshold, and antidepressant re-

sponse to repetitive transcranial magnetic stimulation. J Neuropsychiatry Clin Neurosci 12(3): 376–384
Kubicki S, Herrmann WM, Fichte K, Freund G (1979) Reflections on the topics: EEG frequency bands and regulation of vigilance. Pharmacopsychiatry 12: 237–245
Liddle PF (1997) Dynamic neuroimaging with PET, SPET or fMRI. Int Rev Psychiatry 9: 331–337
Loo C, Sachdev P, Elsayed H, McDarmondt B, Mitchell P, Wilkinson M, Parker G, Gandevia S (2001) Effects of a 2- to 4-week course of repetitive transcranial magnetic stimulation (rTMS) on neuropsychologic functioning, electroencephalogram, and auditory threshold in depressed patients. Biol Psychiatry 49: 615–623
Martin JLR, Barbanoj MJ, Schlaepfer TE, Thompson E, Perez V, Kulisevsky J (2003) Repetitive transcranial magnetic stimulation for the treatment of depression. Br J Psychiatry 182: 480–491
McNamara B, Ray JL, Arthurs OJ, Boniface S (2001) Transcranial magnetic stimulation for depression and other psychiatric disorders. Psychol Med 31: 1141–1146
Merrin EL, Floyd TC (1992) Negative symptoms and EEG alpha activity in schizophrenic patients. Schizophr Res 8: 11–20
Merrin EL, Floyd TC (1996) Negative symptoms and EEG alpha in schizophrenia: a replication. Schizophr Res 19: 151–161
Moser DJ, Jorge RE, Manes F, Paradiso S, Benjamin ML, Robinson RJ (2002) Improved executive functioning following repetitive transcranial magnetic stimulation. Neurology 58: 1288–1290
Nahas Z, Molloy M, Risch SC, George MS (2000) TMS in schizophrenia. In: George MS, Belmaker RH (eds) Transcranial magnetic stimulation in neuropsychiatry. American Psychiatric Press, Washington DC, pp 237–251
Okamura H, Jing H, Takigawa M (2001) EEG modification induced by repetitive transcranial magnetic stimulation. J Clin Neurophysiol 18: 318–325
Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9: 97–113
Overall JE (1972) The Brief Psychiatric Rating Scale in psychopharmacology research. University of Texas, Galveston (Psychometric Lab Reports 29)
Pascual-Marqui RD, Michel CM, Lehmann D (1994) Low resolution brain electromagnetic tomography: a new method for localizing electrical activity in the brain. Int J Psychophysiol 18: 49–65
Pascual-Marqui RD, Lehmann D, Koenig T, Kochi K, Merlo MCG, Hell D, Koukkou M (1999) Low resolution brain electromagnetic tomography (LORETA) functional imaging in acute, first-episode, productive schizophrenia. Psychiatry Res 90: 169–179
Pollock VE, Schneider LS, Lyness SA (1991) Reliability of topographic quantitative EEG amplitude in healthy late-middle-aged and elderly subjects. Electroencephalogr Clin Neurophysiol 79(1): 20–26
Saletu B, Kufferle B, Grunberger J, Foldes P, Topitz A, Anderer P (1994) Clinical, EEG mapping and psychometric studies in negative schizophrenia: comparative trials with amisulpride and fluphenazine. Neuropsychobiology 29(3): 125–135
Schreiber S, Dannon PN, Goshen E, Amiaz R, Zwas TS, Grunhaus L (2002) Right prefrontal rTMS treatment for refractory auditory command hallucinations – a neuroSPECT assisted case study. Psychiatry Res 116(1–2): 113–117
Schutter DJ, van Honk J, d'Alfonso AA, Postma A, de Haan EH (2001) Effects of slow rTMS at the right dorsolateral prefrontal cortex on EEG asymmetry and mood. Neuroreport 12: 445–447
Simpson GM, Angus JW (1970) A rating scale for extrapyramidal side effects. Acta Psychiatr Scand (Suppl) 212: 11–19
Sponheim SR, Clementz BA, Iacono WG, Beiser M (2000) Clinical and biological concomitants of resting state EEG power abnormalities in schizophrenia. Biol Psychiatry 48: 1088–1097
Talairach J, Tournoux P (1997) Co-planar stereotaxic atlas of the human brain. Thieme, Stuttgart

Wassermann E (1998) Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalogr Clin Neurophysiol 108: 1–16

Weinberger DR, Berman KF, Zec RF (1986) Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. I. Regional cerebral blood flow evidence. Arch Gen Psychiatry 43: 114–124

Winterer G, Ziller M, Dorn H, Frick K, Mulert C, Wuebben Y, Herrmann WM (2000) Frontal dysfunction in schizophrenia – a new electrophysiological classifier for research and clinical applications. Eur Arch Psychiatry Clin Neurosci 250: 207–214

Authors' address: Dr. M. Jandl, Department of Psychiatry I, University of Ulm, ZfP Weissenau, Weingartshofer Strasse 2, D-88214 Ravensburg, Germany, e-mail: martin.jandl@medizin.uni-ulm.de