TRANSCRANIAL MAGNETIC STIMULATION (TMS) MODULATES EPILEPTIFORM DISCHARGES IN PATIENTS WITH FRONTAL LOBE EPILEPSY: A PRELIMINARY EEG-TMS STUDY

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Accepted 19 September 2012
Published Online 7 December 2012

Background: TMS is being increasingly used as a noninvasive brain stimulation technique for the therapeutic management of partial epilepsies. However, the acute effects of TMS on epileptiform discharges (EDs, i.e. interictal epileptiform activity and subclinical electrographic seizure patterns) remain unexplored. Objective: To investigate whether TMS can modulate EDs in partial epilepsy. Methods: In Experiment Set 1, the safety of the TMS protocol was investigated in 10 well-controlled by anti-epileptic drugs (AEDs) epileptic patients. In Experiment Set 2, the effects of TMS on EDs were studied in three subjects with intractable frontal lobe epilepsies, characterized by particularly frequent EDs. TMS was applied over the electrographic focus with a circular and a figure of eight coil while recording EEG with a 60-channel TMS-compatible EEG system. The effectiveness of TMS in aborting EDs was investigated using survival analysis and brain connectivity analysis. Results: The TMS protocol was well-tolerated. TMS was an effective method to abort EDs even when adjusting for its latency with respect to ED onset (CMH test, p < 0.0001). While the effective brain connectivity around the epileptic focus increased significantly during EDs (p < 0.01), with TMS administration the increase was not statistically significant. Conclusion: TMS can modulate EDs in patients with epileptogenic foci in the cortical convexity and is associated with reversal of ED-induced changes in brain connectivity.

Keywords: Transcranial magnetic stimulation; electroencephalogram; epileptiform discharges; brain connectivity.

1. Introduction

Brain stimulation is a rapidly evolving technique with multiple therapeutic applications in Neurology and Psychiatry. With regard to epilepsy, deep brain stimulation (DBS) of various subcortical targets, such as the anterior thalamic nucleus, has proved to be an effective means of controlling seizures in drug-resistant patients with partial and secondarily generalized seizures. On the other hand, DBS is an invasive procedure associated with a number of side effects including intracranial hemorrhage, implant site infection, psychic adverse events and cognitive dysfunction. Accordingly, noninvasive techniques, such as transcranial magnetic stimulation

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(TMS) and transcranial direct current stimulation (tDCS) are being actively investigated as a therapeutic modality for epilepsy.\textsuperscript{2,3}

Over the last 15 years, a large number of case reports, small scale uncontrolled and controlled studies explored the efficacy and effectiveness of repetitive TMS (rTMS) in various forms of drug-resistant epilepsies. The accumulated evidence suggests that rTMS induces a modest but statistically significant reduction in seizure frequency and interictal discharges, particularly in the subgroup of patients with epileptogenic foci in the cortical convexity.\textsuperscript{2,3} In the vast majority of these studies, brain stimulation was applied in the interictal state. As a result, the acute effects of transcranial magnetic stimulation on epileptiform electrographic discharges remain largely unexplored. TMS, however, can also be applied in the ictal state in an effort to suppress clinical and electrographic seizures as evidenced by a limited number of pioneering studies.\textsuperscript{4,5}

The present study was designed to extend these latter findings by investigating the acute effects of rTMS on epileptiform electrographic discharges (EDs) in patients with partial epilepsy. The objectives of the study included: (i) safety assessment of a developed brain stimulation protocol for epilepsy, (ii) efficacy assessment of the rTMS protocol in terms of modulating EDs and optimal parametrization of rTMS, and (iii) the exploration of changes in effective brain connectivity as a possible mechanism underly- ing rTMS effects on EDs.

2. Methods

2.1. Subjects

All participants gave informed consent for the procedures, which were approved by an institutional review board and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All subjects passed the transcranial magnetic stimulation adult safety and screening questionnaire (TASS),\textsuperscript{6} save for the epilepsy-related questions. The study was conducted in a stepwise manner as follows.

Experiment Set 1. In the initial set of experiments, the safety profile of the brain stimulation protocol was investigated in a cohort of 10 well controlled by anti-epileptic drugs (AEDs) epileptic patients (six females; median age 28 years, range 18–43) who had been seizure-free for the last 12 months under medication. Eight patients suffered from idiopathic generalized epilepsies (diagnosed as “Juvenile Myoclonic Epilepsy” in six and “IGE with GTCs only” in two) and were under monotherapy with valproate ($n = 6$) and levetiracetam ($n = 2$). The remaining two patients had cryptogenic temporal lobe epilepsy and received monotherapy with oxcarbazepine ($n = 1$) and levetiracetam ($n = 1$).

Experiment Set 2. After establishing the safety of the intervention, the main set of experiments was conducted in three patients (one female; median age 32 years, range 28–35) with drug-resistant symptomatic localization-related frontal lobe epilepsies. Their EEGs were characterized by particularly frequent epileptiform discharges commonly exhibiting secondary bilateral synchrony. The term epileptiform discharges (EDs) was used to describe ictal epileptiform activity, in the form of spikes, sharp waves or spike-wave complexes as well as longer lasting subclinical electrographic seizure patterns.\textsuperscript{7} Seizures with clinical manifestations were a priori excluded from further study because seizure-associated movements were expected to interfere with the stimulation and recording procedure. These patients experienced a median number of two complex partial seizures per week (range: 1–4) despite triple AED treatment (Valproate, levetiracetam, topiramate in case 1, oxcarbazepine, valproate, levetiracetam in cases 2 and 3) at maximal tolerated doses. Seizure etiology included perisylvian syndrome (one case) and head trauma (two cases). In all patients, the epileptogenic focus was localized after performing 24-hour video-EEG monitoring in the hemispheric convexity on the right and was easily accessible to transcranial stimulation.

2.2. EEG–TMS setup

EEG-TMS recordings were performed according to recent methodological guidelines\textsuperscript{8} in an electrically shielded room. All sessions took place between 14:00-17:00 with no preceding sleep deprivation or drug withdrawal challenge. For brain stimulation, a repetitive magnetic stimulator [Magstim Rapid, (Magstim, Dyfed, Wales)] with a circular (Magstim type P/N 9784-00) and a 70mm figure of eight coil (Magstim type P/N 9925-00) was used. Stimulating coils were
positioned on a tripod with a flexible extension arm (Manfrotto Ltd., Bassano del Grappa, Italy) and centered manually over stimulation loci.

In order to minimize the TMS-induced artifact, the minipuncture technique of Julkunen et al. was employed. Briefly, after preparing electrode contacts by rubbing the skin using a wooden stick, the epithelium under the electrode contacts was electrically short-circuited by delivering four punctures per electrode with a custom-made mini-puncturing instrument.

During TMS sessions, EEG was recorded continuously with sixty Ag/AgCl pellet electrodes, specially designed so as to avoid overheating by TMS-induced eddy currents and connected to a TMS-compatible EEG amplifier (eXimia, Nexstim Ltd., Helsinki, Finland). During acquisition, the reference channel was attached to the left mastoid and the ground electrode placed on the left zygomatic bone at a distance of approximately 4 cm from each other. The EEG signals were band-pass filtered from 0.1 to 500 Hz and sampled with a 1450 Hz sampling frequency and 16-bit precision. In order to reduce the TMS-induced artifact, the EEG amplifier was temporarily blocked from 100 µs before to 2 ms after the TMS pulse by a sample-and-hold circuitry.

2.3. Brain stimulation protocol

Magnetic stimuli were delivered in the quiescent interictal state (Experiment Sets 1 and 2) and during epileptiform discharges (Experiment Set 2) with the following parameters:

(i) Location: Stimulation was applied over the area of the electrographic focus (Fp2 and F4 positions of the International 10–20 system).

(ii) Orientation: The optimal orientation of the figure of eight TMS coil in areas beyond the motor cortex has not been investigated in detail. For the purpose of the present study, it was defined as the orientation inducing maximal EEG-TMS responses and was identified in two subjects by positioning the coil over stimulation loci and rotating it in pre-defined angles of 0°–180° at 45° steps (modification of Mills et al.). On the basis of these data, the stimulating coil was oriented 45° to the parasagittal level with current in the central segment flowing toward the midline.

(ii) Stimulus intensity: Experimental and clinical evidence suggests that repetitive electrical stimuli at intensities subthreshold to those eliciting epileptiform bursts are effective in reducing the duration of ictal discharges. The need therefore arises to define precisely the threshold for eliciting epileptiform discharges with single-pulse or repetitive TMS in epileptic subjects. To this end, the following bracketing technique was applied (modification of Mills and Nithi): Starting at 30% maximum stimulus output (MSO), single stimuli at intensities increasing by 10% were given until an epileptiform discharge was recorded. Having thus obtained an approximation of the threshold two further points were defined. First, the maximum intensity at which three consecutive stimuli all failed to produce an epileptiform discharge was found by decreasing SI at 5% steps and designated as lower epileptogenic threshold (LEThr).

Second, the minimum intensity at which three consecutive stimuli all produced an epileptiform discharge was found by increasing the intensity in 5% steps from the lowest level which so far had not resulted in an ED and was designated the upper epileptogenic threshold (UEThr). Mean epileptogenic threshold (METhr) was the arithmetic mean of LEThr and UEThr. Thereby, a precise estimate of the threshold for eliciting epileptiform discharges in patients with epilepsy can be derived. Accordingly, in order to deliver subthreshold stimuli, the stimulus intensity employed in the Experiment Sets 1 and 2 was identical to the LEThr of each individual subject.

(iv) Stimulation frequency and number of stimuli: These two parameters were varied between 0.3–15 Hz and trains of 1–10 biphasic magnetic stimuli, respectively.

(c) Treatment latency: Brain stimulation was applied manually at variable treatment latencies (range 0.5–10 s) after the onset of epileptiform discharges (EDs).

ED duration was measured off-line in a blinded fashion (see e.g. Sec. 2.5) by an experienced clinical neurophysiologist unaware of whether the particular EEG segment belonged to TMS or control group.
2.4. **Statistical analysis**

The first question we addressed in the present study was whether epileptiform discharges are more likely to stop if brain stimulation is administered than if it is not. In order to address this issue, Kaplan–Meier survival curves for the duration of epileptiform discharges (ED) in the absence and presence of TMS were constructed and statistically compared.

As stated in the Brain stimulation protocol section, TMS stimuli were administered at variable treatment latencies after the onset of epileptiform discharges. Therefore, the second question that arises is whether the effects of TMS occur irrespective of whether brain stimulation was given early or late in the course of an epileptiform discharge. In order to address this issue, the experimental design and statistical analysis presented in Ref. 17 was adopted.

Briefly, ED durations after TMS were categorized on the basis of their treatment latency into three equally sized TMS groups: <1 s, 1–4 s, >4 s. For each such TMS group, a respective control group was formed from recordings of each patient consisting of (i) the trials not involving TMS and having ED duration larger than the treatment latency of the TMS group and (ii) the trials involving TMS but in which stimulation was not given up to the time of the maximum treatment latency of the corresponding TMS group. For example, if TMS was administered in a given trial with a treatment latency of 5 s, that trial would be a control for the treatment latency groups of 3–4 s and <3 s, and would itself be in the TMS group with the latency range >4 s.

To be able to compare the ED duration after TMS in the TMS and control groups, we define as treatment latency for each control group the median of the treatment latencies of the corresponding TMS group. In this way, in each trial a “stimulus” was given at the treatment latency in both TMS and control groups. Subsequently, the ED duration after the treatment time was measured and the proportions of EDs that were terminated within 2 s, 2–5 s and >5 s in each group were statistically compared using the Cochran–Mantel–Haenszel test for association between treatment (TMS or control) and ED duration, adjusting for treatment latency.18

Since the data contained multiple observations for each patient, the possibility arises that within-patient correlations may exist. In order to account for this possible effect, data were adjusted for each subject’s average ED duration without TMS.

A third question regarded the optimal stimulation parameters. In order to address this issue we investigated the effects of a number of explanatory variables on the efficacy of TMS by means of the Cox proportional hazards model.19 The investigated explanatory variables included the type of stimulating coil, the stimulating frequency and the number of stimuli. The significance of explanatory variables was tested with standard Wald tests. We tested the explanatory variables separately and in the presence of the other variables. Both main effects and interactions with TMS treatment were examined for each of the explanatory variables. The Cox proportional hazards model was applied using a commercially available statistical package (PASW Statistics 18; SPSS, Chicago, IL, USA), whereas all other statistical analysis was made in MATLAB (2007a, The MathWorks, Natick, MA, USA).

2.5. **Connectivity analysis**

Seeking a physiological basis for the effect of TMS, we decided to evaluate its effect on brain’s connectivity. We wanted to investigate how the brain connectivity changes during ED, and more importantly whether the administration of TMS has an inhibitory effect on this change.

In order to perform a blinded evaluation of ED duration and also to derive a valid brain connectivity measure on ECoG segments containing the TMS, first the TMS artifact was removed. With the utilized experimental setup, the TMS artifact starts at the onset of TMS and has a duration of less than 30 ms. Here, we are interested in retrieving the EEG signal solely after this small time interval. Therefore, we assumed a gap in the signal at the time interval [−10, 40] ms with reference to stimulus onset and developed an algorithm for filling the gap. Specifically, we consider a local state space prediction model, reconstructing points of embedding dimension 50 and predicting with the average mapping of five nearest neighbors. We apply this model for forward multi-step prediction from time −10 ms up to 40 ms (searching for neighbors in the preceding 1000 ms) and backward prediction from 40 ms back to −10 ms (searching for neighbors in...
the following 200 ms), and then weigh the backward and forward predictions in \([-10, 40]\) msec, where the weight for the forward prediction decreases linearly from 1 down to 0, and increases linearly from 0 to 1 for the backward prediction. Note that this is an original contribution adapted to fill the gap at the period of a possible structural change of a complex mechanism, and is somehow close to gap filling of chaotic time series, e.g., see Ref. 20.

An additional pre-processing step was required in rare cases to remove a baseline shift and trend effect of TMS, i.e. the level of the EEG signal was abruptly shifted during TMS followed with a gradual convergence toward its baseline. To correct this we used the available ED-free EEG records containing TMS, and on the basis of these TMS epochs we computed for each channel the average pre-TMS segment to establish the baseline, and the average post-TMS segment, considered as an estimate of the post-TMS trend (for both the trimmed mean excluding the 2.5% smallest and largest values was used). Then for each channel the average post-TMS segment was subtracted from the post-TMS segment of each TMS epoch and to this the corresponding average baseline was added. In this way, the baseline shift and trend was corrected for all TMS epochs, also those containing EDs. This is a simple approach compared to other more advanced schemes for detrending, e.g., see Ref. 21, but it is tailored to our setting. Here, we have available epochs of TMS artifact not containing EDs under the same experimental conditions as for epochs of TMS artifact and EDs. Thus, we use the information of the former to correct the latter. An example of the removal of the TMS artifact, as well as the baseline shift and trend is given in Fig. 1.

For the brain connectivity analysis, we used a standard measure of effective connectivity, the partial directed coherence (PDC). PDC is a frequency-domain measure of direct Granger causality using the Fourier transform of the coefficients of a multivariate autoregressive model (MVAR) estimated from a set of time series. Here, the set of time series is a set of multi-channel EEG segments, and PDC gives the direct effect of one channel to another channel at a frequency \(f\). We consider the bands of interest (0–4 Hz), (4–8 Hz), (8–13 Hz) and (13–30 Hz), and the connectivity measure is the average PDC over the discrete frequencies in the range of each band.

Experience from other studies (e.g., see Ref. 23), as well as pilot simulations on parts of the EEG-TMS records have shown that the estimation of PDC depends upon parameters like the sampling rate of the EEG data and the order of the MVAR model. For the former, we found that downsampling by a factor of 2.
factor of two (725 Hz) was an appropriate trade-off sampling rate, and for the latter we decided to use a fixed order 10 for all simulations, rather than selecting the order for each EEG segment by a criterion such as AIC.

PDC was computed on sliding overlapping windows of length 2 s and sliding step 0.5 s over the whole EEG recording, after TMS removal and possibly baseline correction and detrending. The use of a small sliding step aims at tracing more accurately the start of ED and TMS. PDC profiles were produced for all directed pairs $i \rightarrow j$ from the whole recording that contained three particular epochs of interest: (i) a time interval before the start of ED, called “pre-ED”, (ii) the time interval from the start of ED where no TMS was given, called “EDnoTMS” and (iii) the time interval from the start of TMS given after the start of ED, called “EDwithTMS”. In our control EEG recordings we included EEG segments without EDs but with TMS, and evaluated the change of PDC profiles after administration of TMS. As shown in Fig. 2 for an epoch of EEG without ED and two TMS, there is a lot of variation in the PDC profile but no systematic change in the two directions after the administration of TMS.

3. Results

3.1. Clinical effects

The described TMS protocol was well tolerated by all participating subjects. In both experiment sets, no significant side effects were reported, save for the occurrence of occasional slight dizziness and short-lasting headache. Importantly, no clinical seizures occurred as a direct consequence of the stimulation procedure per se.
3.2. Neurophysiological effects

In patients with well-controlled epilepsy (Experiment Set 1), TMS with the specified parameters did not produce epileptiform EEG discharges (i.e. $\text{LET}_{\text{thr}} = 100\% \text{ MSO}$).

In the three patients with drug resistant epilepsy (Experiment Set 2), a total of 404 single or train stimuli were administered in the quiescent interictal state. Twenty-two epileptiform discharges appeared at 100 and 95% MSO [Fig. 3(c)] and were possibly etiologically related to stimulation (incidence of 5.44%). In these cases, the Lower Epileptogenic threshold was 90% MSO whereas in the remaining cases a 100% MSO SI was used.

From a descriptive point of view, the TMS effects on epileptiform discharges fall into five categories. The first and most important TMS effect in the context of this study is the termination of epileptiform

![Fig. 3. The effect of TMS on epileptiform discharges (EDs). Subfigures depict ED termination (a), ED modification (b), ED relapse (c), ED transient decrease (d) and finally, in rare cases, probable causation of epileptiform discharges by TMS stimuli (e). The vertical errors indicate the time of TMS administration.](image-url)
discharges [Fig. 3(a)]. In addition, TMS induced entrainment of the epileptic activity and modification of the frequency content of EDs [Fig. 3(b)]. Other observed phenomena included epileptiform discharge relapse [Fig. 3(c)], transient decrease of EDs [Fig. 3(d)] and finally, as previously mentioned, probable causation of epileptiform discharges by TMS stimuli [Fig. 3(e)].

From a quantitative point of view, the first question of interest is whether TMS resulted in reduced duration of epileptiform discharges. The graphs in Fig. 4 depict the duration of 135 epileptiform discharges without administration of TMS and of 119 discharges with TMS. The black dots represent the exact timing of stimulation onset and it can be readily appreciated that TMS was applied randomly at various treatment latencies within the epileptiform discharge. The Kaplan–Meier curves, as well as the Cox’ proportional hazard model, show that TMS is associated with a small but statistically significant reduction of discharge duration compared to the control situation, when adjusting for subject and session ($p < 0.022$) (Fig. 4).

The next question was whether the TMS effect on ED duration occurs irrespective of treatment latency. The results of the CMH test suggest that no matter...
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If the stimulation is applied early with a treatment latency of <3 s, the probability of stopping the discharges within 2 s is significantly larger with TMS compared to the control situation (p = 0.0008, see Fig. 5). As corollary, the probability of terminating EDs beyond 5 s is significantly higher in the control group. On the basis of these data, we may conclude that the beneficial effect of TMS is observed irrespective of treatment latency.

Finally, the investigation of the significance of various explanatory variables with a Cox proportional hazards model suggests that a circular coil was significantly more effective compared to a figure of eight coil indicating that a greater critical mass of brain tissue must be stimulated in order to obtain this effect. In addition, low stimulation frequency (0.3 Hz) was significantly less effective compared to higher frequencies (3–5 Hz).

3.3. Statistical analysis on PDC profiles

Several studies have reported that the information flow from the epileptic focus to other cortical areas of the epileptogenic region increases during ED, e.g. see Refs. 24 and 25. We confirmed this in our study as well, and a representative example is shown in Fig. 6 for an epoch containing ED (but no TMS). The tendency is that PDC from the focus in the area of FPz to the channel F2 is larger than vice versa during ED.

However, when for the same patient we give TMS after the start of ED, we observe a decreased effect from the focus channel to other channels of the epileptogenic region, i.e. the difference in the PDC in the two directions is smaller. The follow-up of the example in Fig. 6 but when TMS is delivered after...
Fig. 6. (Continued)

Fig. 7. As in Fig. 6 but when repetitive TMS was given after the start of the first ED (vertical dashed line).
Table 1. Results of statistical inference for the difference in average PDC of the states preED and EDnoTMS, and the states preED and EDwithTMS for selected channel pairs. The parametric confidence intervals are given in the columns labeled "CI", and the \( p \)-value of the paired t-test and Wilcoxon signed rank test (in parentheses) are given in the columns labeled "\( p \)-value".

<table>
<thead>
<tr>
<th>Connectivity</th>
<th>preED versus EDnoTMS</th>
<th>preED versus EDwithTMS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CI</td>
<td>( p )-value</td>
</tr>
<tr>
<td>FPz → F2</td>
<td>((-0.35, -0.07))</td>
<td>0.008 (0.012)</td>
</tr>
<tr>
<td>F2 → FPz</td>
<td>((-0.07, 0.11))</td>
<td>0.667 (0.945)</td>
</tr>
<tr>
<td>FPz → P1</td>
<td>((-0.15, 0.05))</td>
<td>0.305 (0.426)</td>
</tr>
<tr>
<td>P1 → FPz</td>
<td>((-0.21, 0.01))</td>
<td>0.066 (0.126)</td>
</tr>
</tbody>
</table>

The start of the ED is shown in Fig. 7. We notice that for this particular case, ED tends to cease and then relapse, a pattern often but not always occurring as discussed above. The results on PDC show that PDC(FPz → F2) does not appear to be particularly larger than PDC(F2 → FPz) during ED when TMS is given.

To assess statistically whether TMS has an inhibitory effect on the connectivity during ED, we first assign for each directed pair of channels and ED episode a representative connectivity value at each of the three following states: the state before ED (pre-ED), the state of ED when no TMS is given (EDnoTMS), and the state of ED but after TMS is given (EDwithTMS). The representative value is derived from the average of the last five PDC values of pre-ED, and the first five PDC values of EDnoTMS or EDwithTMS. Note that the PDC values included in the computations are from EEG windows that do not belong in the cross-over between states, as shown by the open circles in Figs. 6(b) and 7(b).

The statistical results for one EEG recording (circular coil, 90% SI) containing nine matched preED and EDnoTMS states and eight matched preED and EDwithTMS states are given in Table 1. Even from such small paired samples, we are able to observe a statistically significant increase of the causal effect from the epileptic focus (FPz) to other cortical areas of the epileptogenic region (F2) during ED in the absence of TMS. For example, the \( p \)-value for the parametric paired t-test is 0.008 and for the non-parametric Wilcoxon signed rank test is 0.012. However, when we repeat the same analysis when TMS is given after the start of ED, this causal effect is reduced as can be seen by comparing the confidence intervals for the mean differences in Table 1, and it is no longer statistically significant. For this particular EEG recording, we observe a change due to TMS for the causal effect in the inverse direction, which however is not statistical significant. In contrast, the long-range brain connectivity (FPz to P1 and vice versa) remains relatively unchanged by the effect of TMS.

4. Discussion

The present study was designed to investigate whether TMS can modulate epileptiform discharges in patients with frontal lobe epilepsy. Our study yielded three main findings. First, it is concluded that the described brain stimulation paradigm is a procedure that can be safely applied in patients with well-controlled as well as drug-resistant epilepsies. Second, our results suggest that repetitive TMS can reduce the duration of epileptiform discharges in patients with epileptogenic foci in the cortical convexity and provide an indication of the optimal stimulation parameters for eliciting this effect. Finally, it is proposed that TMS-induced changes in effective brain connectivity may underlie the observed acute effects of repetitive TMS (rTMS) on epileptiform discharges.

Brain stimulation for the termination of epileptiform discharges has a long history. Penfield and Jasper were the first to employ intraoperative electrical stimulation in humans in an effort to abort spontaneous seizures recorded by electrocorticography during brain surgery. More recently, Lesser et al. have elegantly demonstrated that electrical...
stimulation of the neocortex can terminate evoked epileptiform after discharges in patients with drug-resistant neocortical epilepsy.\textsuperscript{17,27} Currently, direct electrical stimulation of the epileptogenic zone is considered a highly promising treatment modality for drug resistant epilepsy.\textsuperscript{28} In the closed-loop version of this technique, an intracranial device detects online an impeding or ongoing seizure and delivers a train of electrical stimuli in order to disrupt the epileptic activity,\textsuperscript{29} whereas in the open-loop version of it, a predetermined schedule of low- or high-frequency stimulation is applied irrespective of the underlying cortical activity.

TMS has been also used as a therapeutic tool in epilepsy. This technique involves the generation of a time-varying magnetic field which penetrates the skull in a painless manner and induces electrical currents within the human brain. The TMS-induced electrical currents result in the trans-synaptic excitation, but also inhibition, of the principal output neurons of the cerebral cortex. The therapeutic applications of TMS are based on the fact that rTMS produces effects that outlast the application of a train of stimuli for minutes or hours. The exact nature of the TMS-induced effects depends on the stimulation parameters including the frequency, intensity and length of time for which the stimulation is applied. It is generally thought that low-frequency rTMS (<1 Hz) reduces cortical excitability,\textsuperscript{30} whereas higher frequencies (>1–5 Hz) enhance cortical excitability, particularly if high intensities are used.\textsuperscript{31} These effects are reminiscent of long-term depression (LTD) and long-term potentiation (LTP), two forms of synaptic plasticity elicited in animal models of cortical circuitry by low- and high-frequency electrical stimulation, respectively. Accordingly, it has been suggested that low-frequency rTMS may exert antiepileptic effects by inducing LTD whereas high-frequency stimulation may act in a proconvulsant manner.\textsuperscript{32}

On the basis of this theoretical framework, a number of open label and controlled studies have examined the antiepileptic effects of rTMS applied in the interictal state. In addition, a limited number of pioneering studies investigated the acute effects of rTMS on seizures and epileptiform discharges. Rotenberg et al.\textsuperscript{5} investigated seven patients with epilepsy partialis continua (EPC) of mixed etiologies. Brain stimulation was applied in high-frequency (20–100 Hz) bursts or as prolonged low-frequency (1 Hz) trains and the EEG was recorded for three of the seven patients. TMS resulted in a brief (20–30 min) pause in seizures in three of seven patients and a lasting (≤1 day) pause in two of seven. The authors concluded that TMS may be safe and effective in suppressing ongoing seizures associated with EPC. In addition, the authors detected and quantified this therapeutic effect during continuous EEG recording thereby proving the potential utility of combined EEG-TMS in seizure treatment.

In a similar vein, our preliminary data, obtained in a cohort of epilepsy patients including three subjects with drug-resistant partial epilepsy, indicate that TMS can be applied with minimal side effects and no apparent worsening of clinical seizures in patients with epilepsy and may result in the termination of epileptiform discharges.

The optimal stimulation parameters detected in the present study merit further discussion. Regarding the optimal frequency of stimulation, it was concluded that 3–5 Hz were significantly more effective compared to lower frequencies of 0.3 Hz. Experimental data from neocortical\textsuperscript{33} and hippocampal\textsuperscript{34} brain slices indicate that stimulation at 0.5–5 Hz is significantly more effective compared to lower frequencies in attenuating epileptiform discharges. Similarly, d’ Arcangelo et al.\textsuperscript{12} observed that 1 Hz stimulation produced maximal decreases in intrinsic optical signal (IOS) associated with ictal synchronization whereas slower and faster (5 and 10 Hz) frequencies proved to be ineffective. In an in vivo model of temporal lobe epilepsy (the kainate model), Rajdev et al. recently reported that electrical stimulation of the hippocampus at 5 Hz was significantly more effective in aborting seizures compared to 60 and 130 Hz groups.\textsuperscript{15} On the other hand, higher frequencies have been reported to be effective in controlling seizures in clinical studies\textsuperscript{3} and warrant further study. It is worth noting that although current experimental and clinical brain stimulation paradigms utilize fixed stimulation frequencies, future approaches may use adaptive neurostimulation strategies for the automatic optimization of stimulation parameters based, for instance, on techniques from the machine learning literature.\textsuperscript{34}

With regard to the stimulus location, we opted to center the stimulating coil over the electrographic focus rather than using a fixed stimulation point (for...
instance the vertex\textsuperscript{35}). Experimental data suggest that placement of the stimulating electrodes in close proximity to the site of seizure onset is a prerequisite for an efficient antiepileptic effect.\textsuperscript{13,36} Although in our group of patients stimulating the electrographic focus was feasible, since the epileptogenic zone was located on the convexity of the frontal lobe, it is clear that in the majority of epilepsy patients the ictal onset zone may not be accessible to transcranial stimulation thereby severely limiting the clinical usefulness of the method. In these cases, it might be worth investigating the effect of deep TMS on epileptiform discharges.

The stimulus intensity is a parameter of critical importance. In the present study, we proposed a method for measuring the epileptogenic threshold (EThr) in individual subjects and subsequently applied intensity levels subthreshold to EThr in accord with previous experimental\textsuperscript{12,13} and clinical\textsuperscript{14} data suggesting that brain stimulation can have both excitatory and inhibitory effects depending, among others, on the employed stimulation intensity. For instance, Yamamoto et al.\textsuperscript{14} reported a decrease in the frequency of interictal discharges with low-intensity (0.5 mA) electrical stimulation of the epileptic focus in a patient with intractable medial temporal lobe epilepsy whereas higher intensities (2 and 7.5 mA) elicited auras and epileptiform after discharges.

One can only speculate about the mechanisms underlying the TMS-induced effects on epileptiform discharges observed in our study. The possibility of an artificial origin can be easily dismissed since the EEG system employed in the present study is a dedicated, TMS-compatible system. In addition, if amplifier saturation was present, phenomena like the entrainment of epileptic discharges as well as, ongoing underlying EEG rhythms would not be observable. Accordingly, it is suggested that TMS induced a transient unresponsiveness in the cortical network supporting electrographic seizure generation.

Theoretically, electrical and magnetic stimulation may elicit an acute antiepileptic effect via three mechanisms: reduction in the excitability of neurons, increased inhibitory neurotransmission, and depression of excitatory neurotransmission.\textsuperscript{37} The detailed in vitro studies of Schiller et al.\textsuperscript{13} indicate that the antiepileptic effects of stimulation were mediated mostly by short-term synaptic depression of excitatory neurotransmission. Notably, the mechanism of LTD which is frequently invoked as the underlying antiepileptic mechanism of TMS applied interictally may not be applicable in the case of acute seizure suppression as it typically operates on a much longer time scale.\textsuperscript{12}

From a different perspective, we hypothesized that, at the network level, the TMS-induced effects on epileptiform discharges may correspond to a restoration of brain connectivity which is pathologically altered during the ictus. A number of recent publications on connectivity and network analysis of epileptic seizures reported that ictal onset is characterized by increased betweenness centrality of a number of neurophysiological parameters, includ-

ing network synchronization, excitability, temporarily varying frequency of brain oscillatory activity, whereas TMS resulted in a global decrease in brain state.\textsuperscript{38} Still, indications of reduced functional connectivity around the epileptic focus after rTMS administration should be treated with caution as the spatiotemporal synchronization topology is complicated.\textsuperscript{41}

TMS has generated hope in the field of epilepsy as a novel neuromodulatory treatment with a number of advantages. It is noninvasive, relatively safe and inexpensive and may potentially induce long-term depression (LTD)-like phenomena and reverse the hyperexcitable state of epileptic foci. However, the prospects of using rTMS in the immediate future
as a therapeutic tool in clinical epilepsy are quite low for a number of reasons. First of all, the results of numerous randomized, sham-controlled or open label clinical studies have proven to be rather unsatisfactory with only a small number reporting significant seizure reduction after the administration of TMS. Second, currently available stimulation paradigms do not produce long-lasting effects on cortical excitability necessitating the frequent repetition of TMS sessions. This is clearly an impractical approach for the management of a chronic disease such as epilepsy. Finally, patients with deep-seated epileptogenic foci (e.g. in the medial part of the temporal lobes or the orbitalfrontal cortex), which constitute a significant part of the drug-resistant population, may not be suitable candidates for TMS treatment. Currently available TMS techniques enable only superficial stimulation of the brain because the intensity of the induced electric field declines rapidly as a function of the distance between the stimulating coil and the targeted structure. Although novel techniques, such as Deep TMS, may prove to be more appropriate for this population, this remains to be investigated. What are then the practical implications of our findings? A possible clinical application of the effect of TMS on epileptiform discharges is that it may serve as a predictor of response to invasive brain stimulation techniques such as DBS or direct electrical cortical stimulation. This, of course, is a hypothesis that needs to be tested in future studies.

In conclusion our results indicate that repetitive TMS can modulate epileptiform discharges in patients with superficial epileptogenic foci and they add to the currently limited literature in this field.

Acknowledgments

The authors would like to thank their patients for their willingness to participate in the study and Petro Julkunen, PhD for his most generous help with the minipuncture technique.

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