The peri-ictal state: cortical excitability changes within 24 h of a seizure

Radwa Badawy,1,2 Richard Macdonell,1,2 Graeme Jackson1,2 and Samuel Berkovic1,2

1 Department of Neurology, Austin Health, Heidelberg, Victoria, Australia
2 Epilepsy Research Centre, Department of Medicine, University of Melbourne, Heidelberg West, Victoria, Australia

Correspondence to: Richard Macdonell, Deputy Director of Neurology, Department of Neurology, Austin Health, Studley Road, Heidelberg, 3084 Victoria, Australia
E-mail: Richard.Macdonell@austin.org.au

In this study, transcranial magnetic stimulation was used to investigate motor cortical excitability changes in the peri-ictal period, in drug-naive new-onset epilepsy patients. Eighty-seven studies were performed on 58 patients (23 with idiopathic generalized epilepsy and 35 with focal epilepsy) within 72 h before or after a seizure. Fifty studies in 35 patients were within 24 h of a seizure. In all 58 patients, an interictal baseline study was performed, at least 14 days from a seizure. Motor threshold and paired pulse recovery curve results obtained at short (2–15 ms) and long (50–400 ms) interstimulus intervals in each hemisphere (at ≤24 h pre- or post-seizure and 24–72 h pre- and post-seizure) were compared against the interictal results and normal control values obtained from 32 subjects. The nature of the seizure (generalized, focal or focal with secondary generalization) was also recorded. Increased motor cortex excitability, measured by decreased motor threshold, increased intracortical facilitation and decreased intracortical inhibition at short and long interstimulus intervals was seen in the 24 h before a seizure. Conversely, decreased excitability occurred in the 24 h after a seizure. These effects were bilateral in tonic-clonic seizures in idiopathic generalized epilepsy and also in secondarily generalized seizures in patients with focal epilepsy. Similar changes were seen in the hemisphere ipsilateral to the seizure focus in focal seizures that did not secondarily generalize, accompanied by complex excitability changes in the contralateral hemisphere. These effects were not apparent in the 24–72 h window. These results show that there are major and prolonged changes in motor cortex excitability in the pre and the postictal 24 h. Increased excitation precedes the seizure by hours and there is a similar period of decreased excitability following a seizure.

Keywords: cortical excitability; seizures; epilepsy; transcranial magnetic stimulation

Introduction

Seizures generally occur without warning and clinically it is largely assumed that the shift between the interictal and ictal states occurs as an abrupt phenomenon. Over recent years, there are growing evidence to indicate that this two-state model is inadequate, and that there is a prolonged transitional peri-ictal phase between the seizure and the interictal state.

Pre-ictal prodromal symptoms such as irritability or headache are frequently reported by patients minutes, hours or even days prior to clinical seizure onset (Delamont et al., 1999). More recently, techniques based on sophisticated EEG analysis have been used to
anticipate or predict seizures by demonstrating EEG changes long before the seizure (Esteller et al., 2005; Iasemidis et al., 2005; Kalitzin et al., 2005; Le Van Quyen, 2005). Quantitative analysis of intracranial EEG (Litt et al., 2001) as well as pre-ictal fMRI studies (Federico et al., 2005) in patients with focal epilepsy also suggest there are prolonged and widespread changes in cerebral function that can begin hours prior to seizure.

Similarly, post-ictal changes have been described with features such as confusion and amnesia being commonly reported by patients following a seizure (Biton et al., 1990; Helmstaedter et al., 1994), making the post-ictal period even more disturbing, for some patients, than the seizure itself. Post-ictal EEG abnormalities are often evident on routine recordings and as such they are more obvious than the pre-ictal changes. They can last for many hours and include regional or diffuse polymorphic delta activity, attenuation of EEG rhythms or activation of focal spikes (Kaibara and Blume, 1988).

Transcranial magnetic stimulation (TMS) has long been used to demonstrate increased cortical excitability in epilepsy patients (Reutens and Berkovic, 1992; Manganotti et al., 2000; Werhahn et al., 2000; Hamer et al., 2005; Badawy et al., 2007), however, these reports are of interictal changes. In the current study, we investigate changes in cortical excitability pre and postictally using TMS methodology. As part of a large systematic study of TMS in new onset epilepsy, we identified TMS measurements that had been performed within 72 h of a seizure. We then retested all these patients a second time at least 14 days from a seizure to explore changes in cortical excitability occurring around the time of the seizure.

Methods

Subjects

Patients were recruited through the First Seizure and Epilepsy Clinics at Austin Health in Melbourne, Australia. The First Seizure Clinic is an acute referral service for patients who present with new onset seizures. The Epilepsy Clinic is a tertiary referral service for the follow up of patients with an established diagnosis of epilepsy. The diagnosis of epilepsy and its sub-syndrome were made by at least two experienced epileptologists on the basis of the clinical history, imaging and EEG findings. Only patients with a confirmed diagnosis of epileptic seizures and a normal neurological examination were included. None of the patients had commenced antiepileptic drugs as a consequence of this presentation, and none had ever previously been treated with antiepileptic drugs.

We performed 259 TMS studies in 129 new onset epilepsy patients. This report is based on the 87 studies (on 58 patients) that were performed within 72 h of a seizure. A repeat study, in a true interictal state, was performed in each of these 58 patients.

Idiopathic generalized epilepsy

Twenty-three patients with idiopathic generalized epilepsy (12 females; mean age: 27 years; range 14–47 years) were included in the study. A diagnosis of idiopathic generalized epilepsy (IGE) required generalized epileptiform abnormalities on EEG or where EEG studies were non-diagnostic, a clear history of either absence or myoclonic seizures in addition to generalized tonic–clonic seizures. All idiopathic generalized epilepsy patients had suffered at least one generalized tonic–clonic seizure. Based on the seizure semiology and EEG findings nine were diagnosed with juvenile myoclonic epilepsy and one with juvenile absence epilepsy. In thirteen patients no idiopathic generalized epilepsy sub-syndrome could be specified.

Focal epilepsy

Thirty-five patients with focal epilepsies (21 females, mean age: 33 years; range 14–52 years) were studied. For a diagnosis of focal epilepsy it was required that the seizure symptomatology or the EEG showed either a left or right-sided lateralization. To avoid direct effects of the epilepsy on motor cortical excitability, patients with electro-clinical features suggesting localization of the focus to the motor strip were not included. Patients with bilateral foci were also excluded.

Twenty-one patients were diagnosed with temporal lobe epilepsy and 14 patients with extra-temporal (frontal or occipital) lobe epilepsy. All these patients underwent a brain MRI. Hippocampal asymmetry, thought to be incidental and non-pathological and not hippocampal sclerosis, was detected in two patients. No abnormalities were found in the remainder. Twenty-six patients with focal epilepsy had a history of at least one secondarily generalized seizure, whereas the remaining nine had only complex partial seizures.

Non-epilepsy controls

The TMS results were compared to those of 32 healthy control subjects (20 females; mean age: 31 years; range 16–73 years) without a history of seizures or other neurological conditions.

Details of the seizures studied

Of the 58 patients with 87 peri-ictal studies, 21 had pre-ictal, interictal and post-ictal studies, 17 had only pre-ictal and interictal and 20 had interictal and post-ictal. Details of the epilepsy syndrome and whether the study occurred within 24 h of a seizure or in the 24–72 h window are shown in Table 1. Eight patients had two pre-ictal studies.

Of the 57 focal seizures examined, 29 were complex partial seizures, two simple partial seizures and 26 were partial seizures that became secondarily generalized.

Table 1 Details of 87 peri-ictal studies performed on 58 patients

<table>
<thead>
<tr>
<th>Time before</th>
<th>Study</th>
<th>Idiopathic generalized epilepsy</th>
<th>Focal epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>after seizure (h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–24</td>
<td>Pre-ictal</td>
<td>9 (8)</td>
<td>17 (14)</td>
</tr>
<tr>
<td></td>
<td>Post-ictal</td>
<td>8 (8)</td>
<td>16 (16)</td>
</tr>
<tr>
<td>24–72</td>
<td>Pre-ictal</td>
<td>7 (7)</td>
<td>13 (9)</td>
</tr>
<tr>
<td></td>
<td>Post-ictal</td>
<td>6 (6)</td>
<td>11 (11)</td>
</tr>
</tbody>
</table>

Numbers refer to studies and numbers in brackets and italics refer to number of patients. Studies performed within 24 h of a seizure were conducted at a mean of 18.9 h before the seizure and 16.5 h post-ictally. Those performed 24–72 h within a seizure were conducted at a mean of 39.5 h before the seizure and 42.3 h post-ictally.
Interictal studies

All 58 patients had a further interictal study performed under baseline conditions. This was done by ensuring 7–9 h of uninterrupted sleep the night before and the results were included in the analysis only if there was at least a 2 week seizure-free period preceding and following the TMS study.

Test–retest variance

A separate group of 20 age- and sex-matched drug naïve patients (10 with idiopathic generalized epilepsy and 10 with focal epilepsy) were studied twice with TMS using a similar time interval between studies (2–4 weeks) to determine normal test-to-test variability in patients with epilepsy. To avoid hormonal effects on cortical excitability, all females in the child-bearing period had the interictal TMS study performed during the same phase of the menstrual cycle in which the seizure occurred (Smith et al., 1999; Hattemer et al., 2006). In addition, all subjects had each test performed at the same time of day (a.m. or p.m.).

Transcranial magnetic stimulation paradigm

All TMS studies were performed by the same operator (RABB) and were performed prior to exposure to antiepileptic medication. During TMS, the subjects sat in a comfortable, reclining chair and a surface electromyographic (EMG) recording was made from the abductor pollicis brevis muscle. The stimulus was delivered to the contralateral cerebral hemisphere using the appropriate direction of coil current flow (anticlockwise for left cortical stimulation and clockwise for right cortical stimulation), using a flat circular 9-cm diameter magnetic coil (14-cm external diameter) with the centre of the coil positioned over the vertex and held in a plane tangential to it using a pair of Magstim 200 magnetic stimulators (Magstim, Whitland, Dyfed, UK). The coil was held in place by a support stand, and its position was regularly checked. Intracortical excitability was studied by paired stimulation at various interstimulus intervals using a Bistim module to connect two stimulators to the coil.

The motor evoked potentials were recorded on an Oxford Medelec Synergy electromyography machine. Filters for the acquisition were set to low frequency of 10 Hz and high frequency of 5 kHz. Sweep speed for threshold determination was 100 ms and the gain was set to 100 μV/div. Once threshold had been determined, the sweep was adjusted to 500 ms and amplitude sensitivity to 5 mV/div. Motor evoked potential amplitudes were measured from peak-to-peak.

Each experimental session lasted for 60–90 min and the following parameters were recorded: (i) Motor threshold was determined in all tested hemispheres while the subject was at rest, verified by continuous visual and auditory EMG feedback. Stimulation commenced at 30% of maximum output and increased in 5% increments until the motor evoked potential was established. One per cent changes in intensity were used to measure the threshold value. Motor threshold was defined as the lowest level of stimulus intensity which produced a motor evoked potential in the target muscle of peak-to-peak amplitude >100 μV on 50% or more of 10 trials (Rossini et al., 1994); (ii) Cortical recovery curves using paired pulse stimulation. In order to construct the long interstimulus interval recovery curves subjects were stimulated at rest, at an intensity 20% above motor threshold using paired stimuli in 50-ms increments at interstimulus intervals of 50–400 ms. The short interstimulus interval curve was constructed at 2, 5, 10 and 15 ms. The first stimulus was given at 80% of motor threshold and the second stimulus 20% above motor threshold. Ten stimuli at 20% above motor threshold without a pre-conditioning stimulus were also given. A minimum interval of 15 s was kept between the delivery of each pair of stimuli. Stimuli were given at randomly selected interstimulus intervals until a total of 10 at each interstimulus interval was achieved.

The recovery curve at longer interstimulus intervals (50–400 ms) was constructed for each hemisphere by using the ratio of the mean peak-to-peak amplitudes of the response to the second stimulus termed the test response and the first stimulus termed the conditioning response at each interstimulus interval measured as a percentage.

In the case of the recovery curve at short interstimulus intervals (2–15 ms), the ratio of the mean peak-to-peak amplitude of the response at each interstimulus interval following the conditioning stimulus given below motor threshold (test response) was expressed as the percentage of the mean motor evoked potential when the test stimulus was given alone without a pre-conditioning stimulus (motor evoked potential) to generate recovery curves for each subject.

The study protocols were approved by the Austin Health Human Research Ethics Committee and written informed consent was obtained from all individuals, including parental consent from those subjects under the age of 18 years.

Statistical analysis

Patients (IGE and focal epilepsy) were assigned to a group (‘pre-ictal’ or ‘post-ictal’) based on whether they were examined pre- or post-seizure. All the patients in the idiopathic generalized epilepsy group had generalized seizures. The focal epilepsy group was further divided based on whether they had secondarily generalized seizures or not. Each group was then further sub-divided based on the amount of time from the seizure (<24 h and >24 h pre- or post-seizure) (Table 1).

In IGE and non-epilepsy controls the results were analysed according to hemisphere dominance assessed according to the Edinburgh Handedness Inventory (Oldfield, 1971). In focal epilepsy, the results were analysed according to the ipsilateral (hemisphere ipsilateral to the presumed seizure focus) and contralateral hemisphere. This was based on EEG findings and/or seizure semiology.

A two-way multivariate analysis of variance ANOVA (2 × 2) test was used with two between subjects factors (type of seizure and time pre- or post-seizure); the dependent variable was the change [pre- or post-seizure minus baseline value at each measure (motor threshold and interstimulus interval)]. This was performed for each hemisphere, in each group. Post hoc analysis with pair-wise paired t-test and Bonferroni correction was used to compare all significant interactions. The analysis was performed on SPSS, 15.0 for Windows®.

The effect size (d) was calculated for the significant results (motor threshold and each interstimulus interval) using the formula:

$$d = \frac{\text{mean of variable (e.g. pre- or post-ictal)} - \text{mean of baseline (inter-ictal)}}{\text{standard deviation of baseline (inter-ictal state)}}$$

Effect size 0.2 was considered small, 0.5 was considered medium and ≥0.8 was considered large (Cohen, 1969). To assess inter-trial variability, Lin’s concordance correlation coefficient test (Lin, 1989) was used to measure the agreement between the two measured motor threshold and interstimulus interval values. Rho-c values <0.5 were considered to indicate poor agreement; values between 0.5 and 0.85 moderate agreement; and values ≥0.85 close agreement between the two trials.
Results

Test–retest variance

There was close agreement between the two trials (performed by a single investigator) on drug naive patients to assess inter-trial variability in motor threshold and at all interstimulus intervals (rho-c ranging from 0.93 to 0.95) and no significant trial-to-trial differences emerged in any of the subject groups (IGE or focal epilepsy).

Inter-hemispheric differences in IGE patients

Analysis of the results of TMS studies in patients with IGE showed no inter-hemispheric differences in either pre or postictal studies. Consequently only the results from the dominant hemisphere are reported.

Effect of timing of the TMS studies

Motor threshold

Non-epilepsy controls

The mean motor threshold in the non-epilepsy control subjects was 56.2 ± 8.7 and is shown in Fig. 1 as the horizontal dashed line.

Pre-ictal: IGE and focal epilepsy

In the IGE subjects studied in the 24-h period preceding a seizure, mean motor threshold was significantly decreased compared with the interictal measurement ($P<0.05$, effect size 0.6), and was significantly lower than the non-epileptic control value ($P<0.05$, effect size 0.4) (Fig. 1A). In patients with focal epilepsy the same pattern was seen in both hemispheres when seizures were secondarily generalized, but only occurred in the ipsilateral hemisphere when the seizures did not generalize, ($P<0.05$, effect sizes 0.3 and 0.5 respectively, Fig. 1B and C) comparing pre-ictal with interictal states. Conversely, in those patients with focal epilepsy whose seizures did not generalize there was a dramatic difference in the contralateral hemisphere with an increase in the mean motor threshold in the <24-h preictal period compared with interictal values and control values ($P<0.05$, effect size 0.3, right data point Fig. 1C).

There was no significant change comparing pre-ictal to interictal mean motor thresholds in any of the groups where the pre-ictal study was 24–72 h before a seizure.

Post-ictal: IGE and focal epilepsy

Mean motor threshold was significantly increased in the IGE subjects studied in the 24-h period following a seizure compared to the interictal measurement and non-epilepsy controls, ($P<0.05$, effect sizes 0.4 and 0.3, respectively, Fig. 1D). In patients with focal epilepsy mean motor threshold was increased compared with the interictal measurement in both hemispheres regardless of whether or not the seizure secondarily generalized ($P<0.05$, effect sizes ranging from 0.4 to 0.6, Fig. 1E and F). All mean motor thresholds, apart from the value in the contralateral hemisphere when seizures did not generalize, were significantly different from the control values. The contralateral hemisphere result did show a trend in the same direction.

There was no significant change comparing post-ictal to interictal motor threshold values in any of the groups where the post-ictal study was 24–72 h after a seizure.

Figure 1  Box plot showing pre-ictal, interictal and post-ictal motor threshold values (mean±SD) for the dominant hemisphere in IGE patients and each hemisphere in patients with focal epilepsy groups divided based on whether the seizures were secondarily generalized or not. The dashed line represents the mean motor threshold value in non-epilepsy controls ($n$=number of studies).
Cortical recovery curves

Idiopathic generalized epilepsy

Four time phases are presented based on the timing of the measurement relative to a seizure. The major effect is seen in the measurements obtained in the 24-h pre- and post-seizure. The measurements 24–72 h from the seizure (Fig. 2A and D) did not differ significantly from the interictal measurements performed 14 days from a seizure (heavy dotted line Fig. 2) and reproduced in a new cohort, our previously reported interictal findings in IGE patients (Badawy et al., 2007). Recovery curves for non-epilepsy controls are shown for comparison with the measured values in Fig. 2 (fine dotted line).

Pre-ictal 1–24 h

In the patients who had a seizure in the 24 h before their study, there was a marked increase in cortical excitability at all points measured (Fig. 2B). This was shown as an increased intracortical facilitation (10 ms and 15 ms interstimulus intervals), \( P < 0.01 \), maximum effect size 2.4 at the 15 ms interstimulus interval, decreased short intracortical inhibition (2 and 5 ms interstimulus interval), \( P < 0.01 \), maximum effect size 1.3 at the 2 ms interstimulus interval) and decreased long latency intracortical inhibition (50–400 ms interstimulus interval), \( P < 0.01 \), maximum effect size 1.9 at the 250 ms interstimulus interval).

Post-ictal 1–24 h

In the patients who had their study in the 24 h after a seizure, there was a marked decrease in cortical excitability at all points measured in the short interstimulus interval study and a remarkable pattern in the long interstimulus interval curves. The pattern was the same as in non-epilepsy controls and the facilitated peaks at 150 and 250 ms interstimulus intervals that return in the 24–72 h measurements and interictically were not present. There was a significant increase in short intracortical inhibition and long latency intracortical inhibition \( (P < 0.01, \) maximum effect size 2.7 at the 250 ms interstimulus intervals) and decrease in intracortical facilitation \( (P < 0.01, \) maximum effect size 1.8 at the 15 ms interstimulus interval).

Focal epilepsy

In patients with focal epilepsy, there was a difference in measured cortical excitability between the ipsilateral and contralateral hemispheres. We have previously reported these changes in the interictal period (Badawy et al., 2007) and these results were confirmed in the current study, with a new cohort (dotted lines Figs 3 and 4). This pattern was the same when measured in the 24–72 h period and interictically 14 days from a seizure (Figs 3 and 4A and D). There were marked differences in how cortical excitability in each hemisphere changed in the 24-h period around the seizure. This depended on whether the seizure was secondarily generalized or not.

Pre-ictal 1–24 h

In the patients who had a seizure in the 24 h before their study, there was a marked increase in cortical excitability \( (P < 0.01) \), at all points measured for the ipsilateral hemisphere regardless of seizure generalization. When the seizure generalized there was...
Figure 3 Pre-ictal, interictal and post-ictal changes in the short interval interstimulus interval recovery curves in each hemisphere in partial seizures that became secondarily generalized and those that did not (ipsilateral signifies the side with the epileptic focus). Ratios <100% indicate inhibition and ratios >100% indicate facilitation (n=number of studies).

Figure 4 Pre-ictal, interictal and post-ictal changes in the long interval interstimulus interval recovery curves in each hemisphere in partial seizures that became secondarily generalized and those that did not (ipsilateral signifies the side with the epileptic focus). Ratios <100% indicate inhibition and ratios >100% indicate facilitation (n=number of studies).
an increase in the contralateral hemisphere (increased intracortical facilitation; maximum effect size 1.9 at the 15 ms interstimulus interval, decreased short intracortical inhibition; maximum effect size 1.0 at the 2 ms interstimulus interval and decreased long latency intracortical inhibition; maximum effect size 1.4 at the 250 ms interstimulus interval, Figs 3B and 4B). When seizures did not generalize the contralateral hemisphere showed complex changes in cortical excitability with decreased excitability seen at longer interstimulus intervals (P < 0.01, maximum effect size 1.2 at the 300 ms interstimulus interval, Fig. 4B), mixed increased intracortical facilitation (10 and 15 ms, P < 0.05, maximum effect size 0.8 at the interstimulus interval of 15 ms) and increased short intracortical inhibition (2 and 5 ms, P < 0.05, maximum effect size 2.0 at the 2 ms) in the short interstimulus interval curves (Fig. 3B).

Post-ictal 1–24 h
In the patients who had their study in the 24 h after a seizure, there was a marked decrease in cortical excitability at all points measured in the short interstimulus interval curve (P < 0.01, maximum effect size 1.7 at the 15 ms interstimulus interval, Fig. 3C) and a loss of the 250 ms peak in the long interstimulus interval curves for the ipsilateral hemisphere (P < 0.01, effect size 2.4) so that the pattern looked like the interictal one for the contralateral hemisphere (Fig. 4C). Like the IGE patients this pattern was similar to the non-epilepsy controls during this 24-h interval.

Cortical excitability decreased at the shorter interstimulus intervals in the contralateral hemisphere of patients studied within 24 h following a seizure only if the seizures were secondarily generalized (P < 0.01, maximum effect size 1.0 at the 15 ms interstimulus interval, Fig. 3C). There were no significant changes in cortical excitability at longer interstimulus intervals post-seizure regardless of whether the seizure generalized or not (Fig. 4C).

Discussion

Previously, we reported an interictal difference in motor cortical excitability in patients with epilepsy, showing bilateral increased cortical excitability in patients with IGE and increased cortical excitability in the hemisphere ipsilateral to the seizure focus in patients with focal epilepsy (Badawy et al., 2007). In the present study, we studied the peri-ictal period and show that there is a further marked increase in cortical excitability which occurs in the 24 h (mean 19 h) before a seizure occurs and that there is a remarkable reduction in cortical excitability during the 24 h (mean 17 h) following a seizure—to at least the level of our control subjects (without epilepsy). This returns to values similar to the baseline interictal state when measured in the 24–72 h on either side of a seizure. The pre-ictal increase in excitability and post-ictal reduction occurs bilaterally in patients with IGE and focal epilepsy with secondarily generalized seizures. In focal epilepsy the contralateral hemisphere acts rather differently if the seizure does not generalize.

An important finding is that the pattern of increased cortical excitability prior to a seizure was the same for seizures that generalized in both IGE and focal epilepsy patients. We observed a bilateral increase in cortical excitability in both types of epilepsy. This widespread increase in excitability is likely to facilitate the generation and spread of seizures within intracortical networks and also facilitate seizure generalization regardless of what the underlying cause of the epilepsy is.

The complex changes within the contralateral hemisphere, observed pre-ictally in the case of seizures that do not generalize, seem to favour increased cortical inhibition. This perhaps serves as protection against seizure spread to this side. However, when this protective mechanism fails or becomes overwhelmed by the epileptogenic events, cortical excitability may increase within the cortical circuits leading to generalization of the seizure. Alternatively, there could be an underlying difference in the structure and function of the hemisphere, leading to pre-disposition to seizures within some patients, this being reflected in secondarily generalized seizures after a uni-hemispheric seizure onset.

Basis of excitability changes

Motor thresholds measured by TMS mainly reflect neuronal membrane excitability, which largely depends on Na⁺ channel conductivity (Mavroudakis et al., 1997). Paired pulse recovery curves used to measure intracortical inhibition at short interstimulus interval (2–5 ms) reflect the activity of GABA-ergic interneurons, probably GABAA receptor mediated, located within the motor cortex (Boroojerdi, 2002). In contrast, inhibition at longer interstimulus intervals (100–400 ms) does not reflect GABAA receptor inhibition, but is more likely to be mediated by changes in GABAergic circuits (Mott and Lewis, 1994; Ziemann et al., 1998; Valzania et al., 1999). An increase in intracortical facilitation has been considered to reflect increased activity within glutamergic circuits but increases in intracortical facilitation may also arise through a loss of GABAA mediated modulation (Fedi et al., 2008).

Based on these hypotheses, our findings suggest that there may be disturbances of both membrane excitability and GABA-ergic and glutaminergic intracortical networks leading to cortical hyperexcitability in a cerebral hemisphere that, within 24 h, will be, or was, involved in a seizure.

Previous studies of pre-ictal TMS

TMS has been used previously to assess cortical excitability changes, shortly prior to seizures in a group of patients with mesial temporal lobe epilepsy, following antiepileptic drug withdrawal (Wright et al., 2006). They found a reduction in short intracortical inhibition and intracortical facilitation in both hemispheres in the patient group that had seizures within 48 h of the TMS study, but not in the group that did not have a seizure. The difference between short intracortical inhibition (at 2 ms interstimulus interval) and intracortical facilitation (at 15 ms interstimulus interval), in the hemisphere ipsilateral to seizure onset, was highly correlated with the time to the next seizure. No differences were found in motor threshold in either group. Even though the patients included in the study were on multiple anti-epileptic drugs which can affect all TMS measures (Ziemann, 2004), increased cortical excitability was only observed in the sub group that developed seizures suggesting that the changes
can be attributed to pre-ictal alterations in cortical excitability rather than to alterations in antiepileptic drug levels. This study did not differentiate between patients who went on to have secondarily generalized seizures and those who did not, which may account for the lack of the inter-hemispheric difference in their patients compared with our findings.

**Post-ictal TMS findings**

We observed a marked reduction in cortical excitability up to 24 h post-ictally for all the measured parameters (motor threshold, short intracortical inhibition, intracortical facilitation and long latency intracortical inhibition). This led to loss of the interictal peaks observed at longer interstimulus intervals in both hemispheres in IGE and the ipsilateral hemisphere in focal epilepsy such that it was similar to the contralateral hemisphere. There has only been one other study using TMS to investigate patients within 48 h following a tonic–clonic seizure (Delvaux et al., 2001). The authors reported a significant increase in motor threshold and decrease in intracortical facilitation in patients compared with controls, with no change in short intracortical inhibition. While the cohort included in their study did not have a confirmed diagnosis of epilepsy, their findings support our results and indicate that cortical excitability is depressed for many hours and probably up to a day following seizure. This would appear to act as a protective mechanism against recurrence of seizures, although the mechanism of this sustained change in cortical excitability is not known. Our results show that this effect is more marked in a hemisphere that was involved in a seizure and so seems to be an effect induced by the seizure rather than something specific to the aetiology of seizure generation.

**Changes related to a seizure**

The neural mechanisms underlying the transformation between the relatively normal interictal brain state and clinical seizures (the ictal transition) are poorly understood. Based on animal studies, the hypothesis has been advanced that seizure initiation depends on a loss of inhibitory control of the epileptogenic zone (Depaulis et al., 1994) with increased excitability of neighbouring neurons facilitating the spread of seizure activity (Knowles et al., 1987; Traub et al., 1987; Pinto et al., 2005). Seizure termination is thought to be modulated by both synaptic excitations and inhibition and is characterized by a strong depolarizing shift (block), hyperpolarization and recovery of neurons in all cortical areas (Pinto et al., 2005). These concepts facilitated the development of techniques used to predict seizures based on non-linear EEG analysis (Esteller et al., 2005; Iasemidis et al., 2005; Kalitzin et al., 2005; Le Van Quyen, 2005) and quantitative analysis of intracranial EEG (Litt et al., 2001). All these studies showed pre-ictal changes in neuronal activity and increased network dynamics that ranged from minutes to hours prior to seizure onset.

Another tool that has been used to investigate changes related to the pre-ictal state is functional MRI. This technique assesses cerebral activity by detecting signal changes related to focal alterations of de-oxyhaemoglobin concentration (Ogawa et al., 1990). This so called blood oxygen level dependent (BOLD) signal is in turn, related to localized neuronal activity, in particular local field potentials (Logothetis et al., 2001) that can be altered with epilepsy. These studies have demonstrated significant BOLD fMRI signal changes occurring several minutes before the onset of seizures that could be localized to the site of the presumed seizure focus, as well as to other brain regions (Federico et al., 2005).

Our data provide further direct evidence supporting the existence of relatively long transitional excitatory and inhibitory phases preceding and following a seizure. These changes in epilepsy networks appear to last up to 24 h on either side of the seizure and are likely to facilitate the sequence of events that lead to a seizure and its termination. After the seizure the demonstrated inhibition, also creates a physiological state over the following 24 h that is likely to reduce the risk of further seizures.

**Acknowledgements**

We thank Dr Mark Newton and the neurologists in the First Seizure Clinic for their help in recruiting the patients and providing input for the study, Dr Sue Finch and the Statistical Consulting Centre at the University of Melbourne for help with statistical analysis of the results, Dr Danny Flanagan for his help and continual support, the EEG technicians at Austin Health and the participants for their time.

**References**


