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Does the region of epileptogenicity influence the pattern of change in cortical excitability?

Radwa A.B. Badawy [a,b,c,*], Simon J. Vogrin [a], Alan Lai [d], Mark J. Cook [a,b]

[a] Department of Clinical Neurosciences, St Vincent's Hospital, Fitzroy, Australia
[b] Department of Medicine, The University of Melbourne, Parkville, Australia
[c] Department of Electrical and Electronic Engineering, The University of Melbourne, Parkville, Australia
[d] Bionics Institute, East Melbourne, Victoria, Australia

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HIGHLIGHTS

- We use transcranial magnetic stimulation to characterize cortical excitability in focal epilepsies.
- Group TMS studies demonstrate that disturbances in cortical excitability are more confined to the affected hemisphere in drug naïve temporal lobe epilepsy.
- Temporal lobe epilepsy can be distinguished from other focal epilepsies early at onset.

ABSTRACT

Objective: To investigate whether cortical excitability measures on transcranial magnetic stimulation (TMS) differed between groups of patients with different focal epilepsy syndromes.
Methods: 85 Patients with focal epilepsy syndromes divided into temporal and extra-temporal lobe epilepsy were studied. The cohorts were further divided into drug naïve-new onset, refractory and seizure free groups. Motor threshold (MT) and paired pulse TMS at short (2, 5, 10, 15 ms) and long (100–300 ms) interstimulus intervals (ISIs) were measured. Results were compared to those of 20 controls.
Results: Cortical excitability was higher at 2 & 5 ms and 250, 300 ms ISIs ($p < 0.01$) in focal epilepsy syndromes compared to controls however significant inter-hemispheric differences in MT and the same ISIs were only seen in the drug naïve state early at onset and were much more prominent in temporal lobe epilepsy.
Conclusion: Disturbances in cortical excitability are more confined to the affected hemisphere in temporal lobe epilepsy but only early at onset in the drug naïve state.
Significance: Group TMS studies show that cortical excitability measures are different in temporal lobe epilepsy and can be distinguished from other focal epilepsies early at onset in the drug naïve state. Further studies are needed to determine whether these results can be applied clinically as the utility of TMS in distinguishing between epilepsy syndromes at an individual level remains to be determined.

1. Introduction

Focal epilepsies are a group of syndromes that comprise approximately 60% of all epilepsies (Banerjee et al., 2009). They are characterized by focal (partial) seizures that are conceptualized as originating within networks limited to one hemisphere which may be discretely localized or more widely distributed (Berg et al., 2010). Focal epilepsies are further sub-divided based on seizure origin into frontal, temporal, parietal or occipital and sub-classified based on seizure type into seizures with retained awareness (previously known as simple partial) and seizures with loss of awareness (complex partial seizures) (Berg et al., 2010). While a genetic basis is thought to underlie some focal epilepsy syndromes (Szyszkowicz et al., 2009), they are mostly considered to be due to an abnormal focal anatomic substrate such as hippocampal sclerosis or an area of cortical dysgenesis (Berkovic et al., 2006).

* Corresponding author at: Department of Clinical Neurosciences, St Vincent's Hospital, 41 Victoria Parade, Fitzroy, Vic. 3065, Australia. Tel.: +61 3 9288 3068; fax: +61 3 9288 3350.
E-mail address: badawyr@unimelb.edu.au (R.A.B. Badawy).

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Focal epilepsy syndromes are characterized by idiosyncratic, highly stereotyped, clinical and EEG manifestations (Fisher et al., 2005). This stereotypy is probably maintained by activity within an epileptic network that is distinct, and dependent on the location and connections of the epileptogenic zone. It is likely that the activity within these networks influences the pattern of disturbances that occur at the level of cortical excitability.

Transcranial magnetic stimulation (TMS) is an excellent non-invasive tool used to measure motor cortical excitability in epilepsy (Reutens and Berkovic, 1992; Werhahn et al., 2000; Hamer et al., 2005; Manganotti et al., 2000; Badawy et al., 2007; Cantello et al., 2000). Previous studies have shown that motor cortical excitability is influenced by epileptic foci distant from it (Werhahn et al., 2000; Hamer et al., 2005) and we previously reported increased motor cortical excitability lateralized to the affected hemisphere in a large drug naive cohort with new onset focal epilepsy originating outside the motor cortex (Badawy et al., 2007). The results in the unaffected hemisphere were similar to non-epilepsy controls.

Here, we evaluated measures of cortical excitability in different cohorts with various focal epilepsy syndromes to determine whether there are specific cortical excitability patterns linked to the region of epileptogenicity (specifically temporal versus extra-temporal lobe epilepsy) at various stages of the disease.

2. Methods

2.1. Participant populations

2.1.1. Patients

The current study included patients with a confirmed diagnosis of focal epilepsy consecutively recruited by screening the databases of the Epilepsy Clinic and Epilepsy Surgery Program at St Vincent's Hospital in Melbourne. These are tertiary referral centres; the first provides the management of patients with epilepsy and the latter aims for the characterization and pre-surgical evaluation of patients with refractory focal epilepsy. None of these patients have been included in our earlier report on focal and generalized epilepsy (Badawy et al., 2007).

Only participants under the age of 45 years were included to avoid prolonged effects of long standing epilepsy and maintain homogeneity across groups. Participants under the age of 14 years were excluded as their normal single and paired pulse TMS values are non-comparable to older participants, nor have been established in children with epilepsy (Garvey and Mall, 2008; Quintana, 2005). This excluded patients with focal epilepsies of childhood such as focal epilepsy with centro-temporal spikes. In addition in order to overcome any potential confounding factors on our results, patients with any suggestion of seizure initiation within the motor area were not included. This was not expected to affect the robustness of changes in TMS measures due to epilepsy because previous studies have already confirmed that motor cortical excitability is influenced by epileptic foci distant from it (Werhahn et al., 2000; Hamer et al., 2005; Badawy et al., 2007).

The diagnoses were made by at least two experienced epileptologists who were unaware of the study based on clinical history, EEG and imaging findings.

The study protocol was approved by the St Vincent's Hospital Human Research Ethics Committee and written informed consent was obtained from each participant including parental consent from those participants under the age of 18 years. This included detailed descriptions regarding the safety of using TMS in patients with epilepsy and the known risk of 0.0–2.8% for single pulse TMS and 0.0–3.6% for paired pulse being more so in patients with intractable and frequent seizures (Schrader et al., 2004).

Patients were categorized based on (Table 1):

2.1.1.1. Syndrome.

(a) Temporal lobe epilepsy (TLE).
(b) Extra temporal lobe epilepsy (extra-TLE).

Patients presented with various combinations of focal seizures with or without retained awareness and/or secondarily generalized seizures.

2.1.1.2. Status at the time of testing. Our previous studies showed that TMS measures differ depending on whether the patient cohorts are studied at onset prior to exposure to anti-epileptic drugs (AEDs), become seizure free after medication or continue to have refractory seizures (Badawy et al., 2010a, 2013). Consequently we further sub-divided our groups into:

1. *Drug naïve new onset epilepsy:* Patients with newly diagnosed epilepsy were recruited on presentation to the clinic and studied with TMS within the same week, prior to any exposure to AEDs.
2. *Refractory seizures:* Patients were considered refractory if they continued to have seizures for at least three years despite trials of at least two different AEDs at therapeutic doses (Kwan and Brodie, 2000; Kwan et al., 2010). This included focal seizures with loss of awareness and unequivocal focal seizures comprising visual, auditory, motor, sensory or autonomic manifestations with retained awareness or secondarily generalized tonic-clonic seizures. Isolated infrequent non-specific vague feelings, uneasiness or brief déjà vu were not considered seizures.
3. *Seizure free:* Patients who did not experience any of the seizures described above for at least 12 months prior to the TMS test.

2.1.1.3. Inclusion criteria.

(a) Syndromic classification required that the seizure symptomatology (specifically characteristics of the aura when consistently present) and the EEG showed lateralization and localization to a certain lobe. The EEG was considered localizing only if definite and prominent sharp-slow discharges were seen consistently over one region either frontal (Fp1-Fz-F3/ Fp2-Fz,F4), temporal (T1-T3/T2/T4), parietal (P3-C3/P4-C4) or occipital (O1/O2). Patients with temporal intermittent rhythmic delta activity (TIRDA) were included in the TLE group only if the activity was consistently recorded over one hemisphere. Non-specific slowing or sharp waves were not considered lateralizing or localizing even if only recorded on one side. Further localizing signs were found on brain MR images. (Imaging was only routinely performed on patients thought to have focal epilepsy. The findings were available for all patients and are summarized in Table 2).
(b) Normal neurological examination.

2.1.1.4. Exclusion criteria.

(a) Suspicion of non-epileptic events (psychogenic non-epileptic seizures, migraine, parasomnias etc).
(b) Patients with an undetermined epilepsy syndrome.
(c) Seizure foci originating in the vicinity of the motor area (seizure semiology or on imaging).
(d) Bilateral seizure foci.
(e) In the drug naïve new onset groups only: any exposure to AEDs prior to the TMS study.
(f) Previous cortical resections or craniotomies.