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REVIEW

TMS, cortical excitability and epilepsy: The clinical impact

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Summary Paired-pulse transcranial magnetic stimulation (ppTMS) is a well-established method for non-invasive measurement of cortical excitability, alterations of which are the core background of epilepsy. For the past 20 years this technique has been extensively used to assess patients with epilepsy. We present here a critical overview of these studies, with emphasis on their translation to the clinical practice.

Contents

Abbreviations: AMT, active motor threshold; CFE, cryptogenic FE; FE, focal epilepsy; IGE, idiopathic generalized epilepsy; JME, juvenile myoclonic epilepsy; LDB, Lafora body disease; LGS, Lennox-Gastaut syndrome; PME, progressive myoclonic epilepsy; RMT, resting motor threshold; TLE, temporal lobe epilepsy; ULD, Unverricht—Lundborg disease.

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Introduction

Epilepsies are a complex group of syndromes characterized by episodic brain dysfunction manifesting as recurrent seizures (Engel, 2006). Admittedly, the underlying process is mediated by changes in both excitatory and inhibitory neural circuits leading to hyperexcitable seizure networks. Sometimes, the primary motor cortex is a crucial part of these networks. More often, it can be influenced at a distance by non-motor epileptogenic areas (Hamer et al., 2005). Besides, cortical area 4 is easily studied by transcranial magnetic stimulation (TMS), i.e. a safe, painless and non-expensive neurophysiologic tool (Macdonell et al., 2002; Schrader et al., 2004; Tassinari et al., 2003). TMS was initially used to evaluate the integrity of the cortico-spinal tract through conduction studies (Barker et al., 1985). Then, it was applied to measuring the excitatory and inhibitory properties of the cortex itself. This relies on several physiologic variables, which, over the past 25 years, proved much informative in terms of both physiology and disease, particularly movement disorders and epilepsy (Cantello et al., 1992; Kujirai et al., 1993; Macdonell et al., 2002; Valls-Sole et al., 1992; Ziemann et al., 1998a). The most robust findings across epilepsy studies came from one of these testing protocols, i.e. paired-pulse TMS (ppTMS) (Badawy et al., 2007; Brodtmann et al., 1999; Cantello et al., 2000; Hamer et al., 2005; Manganotti et al., 2000, 2001a; Werhahn et al., 2000). We will discuss if, how and why these data can be translated to clinical practice.

Paired-pulse TMS of the primary motor cortex

TMS stimuli, delivered through a given stimulating coil to selected scalp locations overlying the primary motor cortex, activate pyramidal neurons mainly trans-synaptically. The resulting response — the motor evoked potential (MEP) — can be recorded from many muscles, including the small muscles of the hand (Rothwell, 1997). Thus, the stimulus required to produce a typical MEP reflects the global excitability/conductivity of cortical inter-neurons, fast corticospinal pathways, as well as spinal motoneurons (Cracco et al., 1999). Paired-pulse TMS (Fig. 1) is much more focussed on the excitability of cortical elements. According to Kujirai et al. (1993), two stimuli pass the same coil, and if the first (conditioning) is sub-threshold for eliciting a MEP, the response to the second (test), supra-threshold stimulus is reduced for interstimulus intervals (ISIs) of 1—5 ms. This is known as ''short-interval intracortical inhibition'' (SICI) (Fig. 1). Kujirai et al. (1993) suggested that suppression occurred at a cortical level, which was confirmed by direct recordings of corticospinal volleys (Di Lazzaro et al., 1998). For ''threshold'', it was originally meant the relaxed motor threshold (RMT), i.e. the stimulus intensity eliciting reproducible MEPs of 50—100 μV occurring in 50% of a cascade of 10—20 consecutive trials given at rest, when the stimulus intensity is increased at 2% or 5% intervals (Rossini et al., 1994). ''Subthreshold'' meant 0.8 × RMT, and ''suprathreshold'' 1.2 × RMT, which landmarks were the most often used. Some authors however used the ''active'' motor threshold (Rothwell, 1999), or different threshold fractions (Awiszus, 2003; Mills and Nithi, 1997). SICI is thought to reflect very complex inhibitory activities in the context of the primary motor cortex. The most acknowledged contribution (or the final path) is however activation of GABA-ergic cortical inter-neurons, and particularly of $GABA_A$ receptor-mediated effects (Boroojerdi, 2002; Inghilleri et al., 1996; Kujirai et al., 1993; Ziemann, 2003).

At ISIs 10—20 ms, the test response is augmented. This is known as intracortical facilitation (ICF) (Fig. 1), which in turn is thought to be due to complex activation of cortical excitatory inter-neuronal circuits, among which the glutamate-related effects are the most recognized (Inghilleri et al., 1996; Kujirai et al., 1993; Ziemann et al., 1995, 1996), notably mediated by the N-methyl-D-aspartate

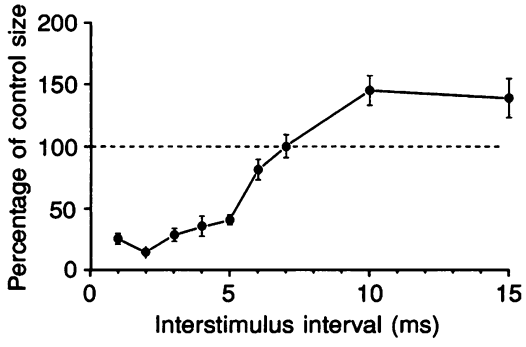

Figure 1 Reproduction of the original corticocortical inhibition and facilitation curves by Kujirai et al. (1993). Group data from patients and controls. Bars represent SEM. ISI, interstimulus interval; MEP, motor-evoked potential.
Source: Taken with permission from Kujirai et al. (1993). John Wiley & Sons Ltd Publishers.

(NMDA) receptor (Ziemann et al., 1998b). However, there is evidence that ICF may not be an exclusively cortical phenomenon (Di Lazzaro et al., 2006). Recently increased ICF was found in people with $GABA_A$ receptor mutations suggesting a role for $GABA_A$ circuits as well (Fedi et al., 2008).

Though a focal, figure-of-eight coil was originally used, SICI and ICF can be easily and reliably measured through the routine circular coil (Badawy et al., 2011).

Another interesting variable is the ''long-interval intracortical inhibition'' (LICI), occurring for longer ISIs (50—400 ms). Indeed, Valls-Sole et al. (1992) found that a suprathreshold conditioning stimulus suppressed a later identical stimulus, if the ISI was between 50 and 200 ms, or up to 400 ms (Badawy et al., 2007; Brodtmann et al., 1999). Because the spinal H reflex was unchanged, the effect was thought to be cortical. LICI is most likely mediated by slow inhibitory post-synaptic potentials activated via $GABA_B$ circuits (Valzania et al., 1999; Werhahn et al., 1999; Ziemann et al., 1998a).

Additional paired-TMS methods were then developed to investigate the inputs to the primary motor cortex from other areas of the brain such as the contralateral M1 (Ferbert et al., 1992), the cerebellum (Ugawa et al., 1995), the premotor cortex (Civardi et al., 2001) and the posterior parietal cortex (Koch et al., 2007). So far, applications to epilepsy were somehow limited (Lappchen et al., 2011).

Safety

The only absolute contraindication to TMS is the presence of metallic hardware in close contact to the discharging coil (such as cochlear implants, or an internal pulse generator or medication pumps). In such instances there is a risk of device malfunctioning (Rossi et al., 2009).

Paired-pulse TMS is generally accepted to be safe in patients with epilepsy. According to the review by Schrader et al. (2004), the crude risk of an associated seizure would range from 0.0 to 3.6%. However, ''in most cases, doubt was expressed in the original reports as to whether the seizures were induced by TMS or merely coincidental'' (Schrader et al., 2004).

Reliability and reproducibility

TMS bears a consistent variability, that encompasses the ppTMS measures of interest here (SICI, ICF and LICI). Most data originate from studies in healthy subjects, where for instance Boroojerdi et al. (2000) described a high intersubject compared to intersession and interinvestigator variability of SICI and ICF. In general, ICF was less variable than SICI. This is consistent with other studies using a similar experimental approach (Maeda et al., 2002; Wassermann, 2002). Orth et al. (2003) suggested that variability could be somewhat reduced if the conditioning stimulus was referred to the individual threshold for SICI or ICF. Though to a lesser degree, intersession variability was found relatively high as well, which would be justified by differences in motor threshold determination, coil positioning, test MEP amplitudes or number of MEPs in each trial (Boroojerdi et al., 2000; Orth et al., 2003). Since intersubject variability is particularly confounding when different subject

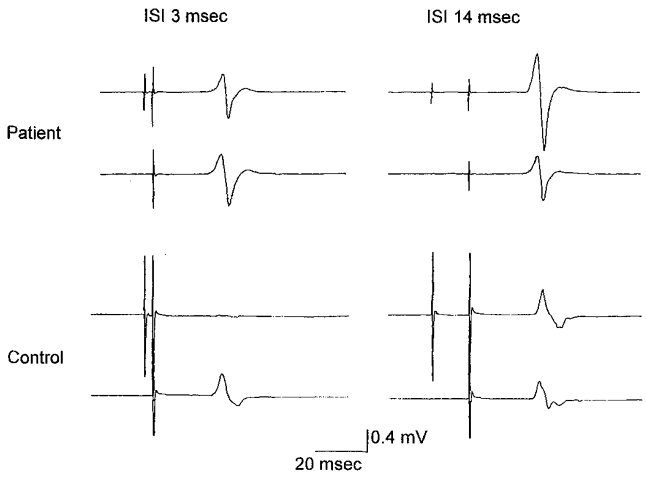

Figure 2 Paired-pulse TMS. Example of lack of inhibition at ISI 3 and excess facilitation at IS1 14 in a patient as compared with a control. Upper tracing: conditioned motor-evoked potential. Lower tracing: control motor-evoked potential.
Source: Taken with permission from Cantello et al. (2000). John Wiley & Sons Ltd Publishers.

groups are compared, it was thought to be more appropriate to assess SICI and ICF in the same group between/among subsequent experimental sessions. In fact, group averages of ppTMS variables did not show significant differences on repeated sessions in both healthy controls and patients with epilepsy (Badawy et al., 2012a). Thus, this testing protocol can be useful for longitudinal studies in groups of patients.

Studies in epilepsy: a criticism

Over the last 20 years, many investigators used ppTMS to study patients with epilepsy (Macdonell et al., 2002; Tassinari et al., 2003; Ziemann et al., 1998b). Critically, one definite conclusion was that, among the many TMS variables, paired-pulse TMS itself was the most suited to disclose cortical excitability changes in this particular context (Cantello et al., 2000) (Fig. 2). However, the overall results were often mixed and contradictory, though a defective SICI (or an exaggerated ICF) were reported in many instances (review in Tassinari et al., 2003) (Fig. 2). Three factors appear most responsible for the inconsistencies, i.e. (a) recruitment of drug-treated patients (b) methodological differences between studies (c) poor correlation of the TMS to the clinical variables, such as for instance the neuroimaging/EEG findings or the drug serum level (Table 1). Possibly, the most severe distortion arose because of the drug effects. Indeed, antiepileptic drugs (AEDs) do affect cortical excitability (Ziemann, 2003). Yet, most investigations were performed on patients taking a variety of anticonvulsants, alone or in combination. This approach seriously undermined the understanding of the ''natural'' behaviour of SICI, ICF and LICI in different patient populations (Cantello et al., 2000; Gianelli et al., 1994; Hamer et al., 2005; Manganotti et al., 2000, 2001b; Reutens and Berkovic, 1992; Werhahn et al., 2000).

Table 1 Characteristics of the main paired-pulse TMS studies in patients with epilepsy. AMT, active motor threshold; CFE, cryptogenic FE; FE, focal epilepsy; IGE, idiopathic generalized epilepsy; JME, juvenile myoclonic epilepsy; LDB, Lafora body disease, LGS, Lennox-Gastaut syndrome; PME, progressive myoclonic epilepsy; RMT, resting motor threshold; TLE, temporal lobe epilepsy; ULD, Unverricht—Lundborg disease.

First author and year	Sample size	Syndromic diagnosis (yes/no)	Seizure diagnosis (yes/no)	Seizure frequency	Refractoriness	EEG/video EEG data (yes/no)	Imaging data (yes/no)	Correlation with EEG	Treatment detail (yes/no)	Drug serum levels (yes/no)	Original Kujirai's stimuli (yes/no)	Monophasic vs biphasic stimulator (M/B)	ISI (ms)
Badawy et al. (2006)	15 IGE 15 FE	Yes	Yes	Not possible	No treatment	Yes	Yes	Yes	No treatment	No treatment	Yes	M	1, 2, 5, 10, 15 200, 250, 300
Badawy et al. (2007)	35 IGE 27 FE	Yes	Yes	Not possible	No treatment	Yes for diagnosis	Yes	No	No treatment	No treatment	Yes	M	1, 2, 5, 10, 15 200, 250, 300, 400
Badawy et al. (2009a)	23 IGE 35 FE	Yes	Yes	Not possible	No treatment	Yes for diagnosis	Yes	No	No treatment	No treatment	Yes	M	2, 5, 10, 15 50—400 (50 increm.)
Badawy et al., 2010	6 PME 19 JME	Yes	Yes	Yes	Yes (PME and refractory JME)	Yes for diagnosis	Yes for diagnosis	No	Just list	No	Yes	M	2, 5, 10, 15 50—400 (50 increm.)
Badawy et al., 2012a	13 IGE 11 FE	Yes	Yes	Not possible	No treatment	Yes	Yes	No	No treatment	No treatment	Yes	M	2, 5, 10, 15 50—400
Badawy et al., 2012b	18 LGS	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	M	2, 5, 10, 15, 100—300
Badawy et al. (2013b)	95 IGE 62 FE	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	M	2, 5, 10, 15, 100—300
Badawy et al. (2013c)	137 IGE	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	M	2, 5, 10, 15, 100—300
Canafoglia et al. (2010)	10 ULD 5 LDB	Yes	Yes	Yes	Yes	Yes for diagnosis	No	No	Yes just a list	No	Yes but 90% AMT/120% RMT	B	1, 2, 3, 4 5, 6, 10, 15
Cantello et al. (2000)	18 CFE	Yes	Yes	Yes	Most part	Yes	Yes	Yes	Yes	Yes	Yes	M	1, 2, 3,4, 5, 6, 8, 10, 12, 14, 16
Delvaux et al. (2001)	18	No	Yes	1 GM	No treatment	Yes	Yes	No	No treatment	No treatment	95%/125% RMT	M	1—10 by 1 ms steps 10—20 by 5 ms steps
Groppa et al. (2008)	25 IGE	Yes	Yes	Yes	No	Yes	No	Yes	YES	No	Yes	M	2, 15
Hamer et al. (2005)	23 FE	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	75% RMT/1.5 mV	M	2, 3, 10, 15
Klimpe et al. (2009)	15 IGE 10 FE	Yes	Yes	Yes	No treatment	Yes	Yes	No	No treatment	No treatment	Yes	M	2, 12
Lappchen et al. (2008)	22 FE	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	M	3, 10
Lappchen et al. (2011)	18 FE	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	IHI	M	8
Manganotti et al. (2000)	15 JME	Yes	Yes	Yes	No	Yes	No	No	Yes	No	95% AMT/120% RMT	M	1, 2, 3, 4, 5, 6, 10, 15, 20, 25, 30 30, 50, 70, 100, 125, 150, 200, 250, 300, 400
Manganotti et al. (2006)	10 JME	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	70%/120% RMT	M	1, 2, 3, 4, 10, 15
Strigaro et al. (2013)	15 IGE	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	M	3, 4, 12, 14
Valzania et al. (1999)	12 PME	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	110%/110% RT	Cadwell high speed magnetic stimulator	50, 100, 150 and 200 ms
Varrasi et al. (2004)	21 FE	Yes	Yes	Yes	No treatment	Yes	Yes	Yes	No treatment	No treatment	Yes	M	2, 3, 14, 16
Werhahn et al. (2000)	15 FE	Yes	Yes	Yes	Missing	Yes	Yes	No	Yes (past)	No current treatment	75%/1—2 mV	M	2, 3, 4, 7, 10, 15
Wright et al. (2006)	18 TLE	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	M	2, 3, 12, 15

Drug-naïve studies

Some fog-dispelling information came from selected groups of drug-naïve patients.

Idiopathic generalized epilepsy (*IGE*): SICI was substantially reduced in drug-naïve patients with IGE compared to controls, particularly in patients with juvenile myoclonic epilepsy (JME) (Badawy et al., 2007; Manganotti et al., 2000, 2001a). While these studies reported no change in ICF, Cantello et al. (2006) reported a significant ICF increase in a group of eight patients, 4 of whom had a diagnosis of juvenile absence epilepsy (JAE). LICI was also found to be significantly reduced in untreated patients with IGE, with a maximum facilitation observed at ISIs of 250—300 ms (Badawy et al., 2007; Brodtmann et al., 1999). Apparently, contrasting findings came from the study of Delvaux et al. (2001) in patients having experienced their first grand mal seizure. However such group had no precise classification and was deemed to be ''certainly not representative of a general population of epileptic patients'' (Delvaux et al., 2001).

Focal epilepsy (*FE*): Varrasi et al. (2004) were the first to study drug-naïve cryptogenic FE patients ($n = 21$). They found that SICI was reduced bilaterally in one-third of them, which had a positive correlation to the amount of interictal spike activity on the EEG (Varrasi et al., 2004). Badawy et al. (2007), in a slightly larger sample with extramotor epileptogenic areas ($n = 27$) did reproduce this finding. Moreover, they were able to show that reduction of SICI prevailed over the hemisphere where the epileptogenic ''focus'' was located on the basis of the overall clinical assessment. The only group that analyzed LICI in patients with untreated FE consistently demonstrated a significant increase in cortical excitability at the 250 and 300 ms ISIs compared to controls. They also reported a significantly higher excitability in the hemisphere with the ''focus'', as compared with the contralateral side (Badawy et al., 2007).

Results in focal epilepsy support the view that epileptogenic areas situated at a distance (e.g. in the temporal lobe) do affect the physiology of the primary motor cortex (Cantello et al., 2000; Hamer et al., 2005). EEG-fMRI studies (Federico et al., 2005; Tyvaert et al., 2008) in patients with cortical malformations have revealed blood oxygen level-dependent (BOLD) signal changes associated with interictal (Federico et al., 2005) and ictal discharges (Tyvaert et al., 2008) in and around the lesion and at distant cortical areas, in some cases involving frontal cortex and specifically the rolandic area. The direct or indirect involvement of the motor area is not surprising considering the diffuse and highly interconnected motor network in the human brain and the common motor seizure phenomenology. Consequently, ppTMS of cortical area 4 is currently considered to be a meaningful index of cortical excitability in FE.

Independent laboratories confirmed the value of ppTMS in documenting altered inhibition in the epileptic cortex in cross-sectional studies. According to the present understanding, it is GABA-ergic inhibition to be impaired as primary detected by SICI that is thought to reflect GABA-A receptor-mediated effects. However, LICI measures are affected as well, reflecting abnormalities in GABA-B receptor-mediated inhibition. This disturbance appears bilateral in IGE, while it prevails in the affected hemisphere in FE. Though this concept is classic knowledge in the animal model, ppTMS quantifies it in groups of intact patients. Moreover, a cortical hyper-excitability profile was found in the asymptomatic/unaffected siblings of patients with focal epilepsy and was more prominent in siblings of patients with generalized epilepsy. These alterations suggest an underlying epileptic trait of increased susceptibility in families with epilepsy (Badawy et al., 2013b).

A conceptual limit of this information is however the finding of similar ppTMS changes in a variety of neuropsychiatric disorders: for example, deficits in TMS measures of cortical inhibition have been reported in schizophrenia (Daskalakis et al., 2002) and Tourette syndrome (Orth et al., 2005). Consequently, ppTMS bears a low positive and negative predictive value, particularly in patients with focal epilepsies, which limits its current application as an individualized diagnostic test.

Cortical excitability fluctuates

Paired-pulse TMS studies showed evidence of a highly dynamic variability in cortical inhibition in relation to seizures and factors known to increase seizure risk.

Sleep—wake cycle

Admittedly, the clinical and EEG manifestations of epilepsy are prone to diurnal fluctuations related to the sleep—wake cycle. This is particularly seen in all forms of IGE, where there is a predilection for seizures and epileptiform EEG discharges to occur on or soon after awakening (Fittipaldi et al., 2001). In the first instance, cortical inhibition was found to vary across the sleep—wake cycle in healthy individuals. Decreased MEPs amplitude (Manganotti et al., 2004a,b) and increased SICI (Manganotti et al., 2001a) were reported during drowsiness, while a dramatic enhancement of SICI during non-rapid eye movement (NREM) sleep stages 3 and 4 was observed (Salih et al., 2005). One study investigating circadian variability in cortical excitability in drug naïve patients with epilepsy and controls reported that in patients with IGE, and particularly with JME, there was decreased SICI and LICI early in the morning compared to the afternoon (Badawy et al., 2009b). The absence of similar findings in another cohort with treated JME (Pfutze et al., 2007) may well be a medication effect. No time of day related changes were seen in patients with FE or in non-epilepsy controls (Badawy et al., 2009b), however a major decrease in SICI was reported during NREM sleep in FE (Salih et al., 2007). Sleep deprivation is a powerful activator of seizures in nearly all types of epilepsy (Gastaut and Tassinari, 1966). Paired pulse TMS studies provided direct evidence of increased cortical excitability with sleep deprivation. Minimal reduction of SICI (Civardi et al., 2001) and LICI (Badawy et al., 2006) following sleep deprivation were reported in healthy subjects, but in epilepsy this effect was much more robust. Increased cortical excitability was found in JME (Manganotti et al., 2006), IGE and FE patients (Badawy et al., 2006).

Menstrual cycle

In many women with epilepsy, seizure exacerbation occurs during the peri-menstrual or peri-ovulatory phases or during the entire second half of menstrual cycle (Herzog, 2008). TMS studies reported that, in normal women, cortical inhibition was reduced (predominantly increased ICF) during the follicular (pre-ovulatory) phase compared to the luteal (pre-menstrual) phase (Smith et al., 1999, 2002). Conversely, cortical excitability was higher during the luteal phase in women with known catamenial epilepsy (Hattemer et al., 2006).

Peri-ictal changes

There is some evidence from quantitative analysis of intracranial EEG (Litt et al., 2001) as well as EEG-fMRI studies (Federico et al., 2005), to suggest peri-ictal changes lasting for minutes to hours at the most. Paired pulse TMS studies provided the first direct human evidence for prolonged peri-ictal cortical excitability changes. Short and long ICI were markedly reduced and ICF markedly increased in patients examined in the 24 h (mean 19 h) before a seizure and then there was a remarkable reduction in cortical excitability during the 24 h following a seizure — to at least the level of control subjects without epilepsy. Values similar to the baseline interictal state were observed when measured in the 24—72 h on either side of a seizure. Furthermore, the preictal increase in excitability and postictal reduction occurred bilaterally in patients with IGE and FE with secondarily generalized partial seizures. In FE the contralateral hemisphere acted rather differently if the seizure remained partial and did not generalize. In this case, there was decreased excitability at longer interstimulus intervals, mixed increased ICF and increased SICI, with the overall picture seeming to favour inhibition, presumably as a protective mechanism to stop seizure spread to that side (Badawy et al., 2009a). Similarly, a reduction in SICI and ICF in the hemisphere ispilateral to the seizure onset was detected in patients with mesial temporal lobe epilepsy following antiepileptic drug reduction in a pre-surgical inpatient admission who had seizures within 48 h but not in the group who did not have a seizure (Wright et al., 2006). The difference between SICI (at 2 ms ISI) and ICF (at 15 ms ISI), in the hemisphere ipsilateral to seizure onset, was highly correlated with the time until the next seizure (Wright et al., 2006) (for review Richardson and Lopes da Silva, 2011). The preictal excitability changes detected by TMS need further studies to assess its clinical contribution to the identification of patients at risk of seizures and eventually its role in the anticipation of seizures in a context of an effective stimulation-based paradigm for the seizure control (Kalitzin et al., 2010; Richardson and Lopes da Silva, 2011).

Cortical excitability and the drug response

Anti-epileptic medication

Despite significant advances in the therapy of epilepsy over the last decades, almost 30% of patients with epilepsy are refractory to drug treatment and continue to have seizures (Kwan and Brodie, 2000). The fact that in many patients with intractable epilepsy, the seizures are refractory from the onset suggests that intrinsic factors are involved in intractability (Arroyo et al., 2002). This is further supported by the differences in treatment outcomes observed in patients with a seemingly identical diagnosis and drug choice. Nevertheless, drug resistance in other patients may develop during the course of epilepsy after an initial positive response, suggesting that epilepsy related acquired changes might be the cause of refractoriness (Kwan and Sander, 2004).

TMS studies suggest that the main disturbance observed in epilepsy is reduced intracortical inhibition. This was shown to normalize with AED use only in patients who became seizure free but not those who continued to have seizures (Badawy et al., 2010a). This effect occurred irrespective of clinical factors such as type of epilepsy, age, age of seizure onset and seizure type or frequency or medication related factors such as the type, known mechanism of action or serum level of AEDs (Badawy et al., 2010a). As commonly used AEDs have different putative key mechanisms of action, this suggests that they may act on a final common pathway to restore the disturbance in cortical excitability to normal levels. Failure of this process to occur may be the reason why patients with refractory epilepsy continue to have seizures. This provides an essential starting point to start developing truly anti-epileptic therapies rather than the currently available medications which have mainly been aimed at suppressing initiation of or propagation of seizures rather than the processes leading to epilepsy (Pitkanen, 2010). One TMS study addressed this in a longitudinal study on a cohort of patients with new onset IGE and FE (Badawy et al., 2013a). The patients were followed up for three years and studied with TMS before, early after starting medication and then at the end of the follow period. When the refractory groups were studied early after treatment, there was still evidence of decreased SICI and LICI. The only change from the initial study was seen in the contralateral hemisphere in the refractory group with FE. This was in the form of decreased LICI. On the other hand, SICI and LICI in the well-controlled groups returned to normal levels. When the refractory cohorts were studied after 30 months of medication, hyper-excitability extended to involve all the long ISIs in both hemispheres of patients with IGE and FE rather than the dips to near normal values at 100 and 200 ms seen in the drug-naïve and early post-treatment studies. In addition, at 30 months, the contralateral hemisphere in the refractory FE group showed evidence of reduced SICI now as well. These results suggest that refractory seizures are associated with progressive changes in GABA-ergic inhibition. These changes possibly reflect altered receptor properties or disturbed receptor interactions within the inhibitory intracortical circuits. In FE this change starts in the hemisphere with the seizure focus and extends to involve the unaffected hemisphere over time, leading to progressive GABA-ergic dysfunction and increased cortical excitability. From this study it seems reasonable to conclude that recurrent seizures are associated with progressive alterations within intracortical circuits (Badawy et al., 2013a). Thus it seems more beneficial to consider early intervention to prevent these changes from occurring.

Monitoring response to therapy

Medication is the first line of approach for managing patients with epilepsy but it can take months, or years to identify the best drugs for any given individual. Response to AEDs is highly variable among patients with regards to efficacy and tolerability even in patients with a seemingly identical diagnosis and drug choice. Therefore the only method currently available is essentially trial and error modified by the neurologists' expertise. A recent study that systemically investigated the relationship between AED use and seizure control in patients with IGE and FE (Badawy et al., 2010a), showed that normalization of SICI and LICI occurred as early as four weeks after starting medication in patients who became seizure free, while it remained reduced in those with ongoing seizures. The results provide evidence that the effect of AEDs on excitability measures correlates with seizure control.

A large scale study is needed to validate TMS as a useful objective tool that predicts efficacy of anti-epileptic therapies. Moreover, there is evidence that TMS may also have the potential to be a reliable marker for response to other forms of anti-epileptic therapy such as surgery (Kamida et al., 2007), vagal nerve stimulation (Di Lazzaro et al., 2004), continuous anterior thalamic deep brain stimulation (Molnar et al., 2006) and the ketogenic diet (Cantello et al., 2007).

Conclusions

Paired-pulse TMS is an emerging tool which provides novel information on the pathophysiology, clinical course and drug response of epilepsy. It translates to the intact patient an electrophysiological approach that was previously bound to experimental models of epilepsy. The alterations seen with ppTMS must be carefully related to the clinical variables, since they have a relatively low specificity. For the moment, the practical ppTMS value is limited to analysis of patient groups due to excess inter-individual variability. Technical/methodological refinements are however likely to offer a higher resolution, at the single-individual level, in the near future.

Conflict of interest

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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