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The Clinical Application of Transcranial Magnetic Stimulation in the Study of Epilepsy

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1. Introduction

Several methods can be used to treat patients with epilepsy: antiepileptic drugs(AED), surgery and neuromodulation. AED is the most common method and also the first choice in the treatment of epilepsy. However, some patients are drug-resistant, or encounter severe adverse effects. In this case, surgery is an alternative to drug therapy for part of these patients. But surgery has several drawbacks: one is its invasive, the other is its high cost, and the third is its requirement for highly equipped medical devices to delineate the epileptogenic zones. These factors limit its wide use in the clinical field.

Epileptic conditions are characterized by an altered balance between excitatory and inhibitory influences at the cortical level(Tassinari et al.,2003). Antiepileptic drugs work by counteracting such imbalance with different mechanisms(Kwan et al.,2001). It is well known that the excitability of cortical networks can be modulated in humans by trains of regularly repeated magnetic stimuli(Wassermann&Lisanby,2001). Therefore, Repetitive transcranial magnetic stimulation (rTMS), a noninvasive and easily applied technology, could even have therapeutic effect in epileptic patients. Although some conflicting results have been reported, growing evidence shows that low-frequency (<1Hz) rTMS (slow rTMS) can significantly reduce seizure frequency and interictal epileptiform discharges. In this chapter, we aim at providing the reader with the most recent information on the application of TMS in epileptic conditions.

This chapter is composed of 6 sections. First, the different ways and parameters that TMS can be used to investigate cortical pathophysiology are introduced. According to the patterns of stimulation, TMS can be divided into at least 3 categories: single-pulse TMS (sTMS), paired-pulse TMS (pTMS) and repetitive TMS (rTMS). Each TMS may reflect different brain cortical functions or have different physiologic effects. The parameters used as TMS study include motor evoked potential (MEP), motor threshold (MT), cortical silent period (CSP), intracortical inhibition (ICI) and intracortical facilitation (ICF). These parameters can reflect the functional state in motor cortex and motor pathway in different ways.

The second section will discuss the possible antiepileptic mechanisms of rTMS in four aspects: electrophysiology, neurotransmitters, ion channel structure and function, as well as neuronal insults.

The third section will refer to two issues: the effects of different AEDs on TMS parameters; the relationship between the changes of TMS parameters and corresponding AED serum

concentrations. The available data suggest that TMS may be a promising tool both in clarifying still-debated mechanisms of action of some AEDs and in optimizing the treatment of patients affected by epileptic seizures.

We will review the therapeutic effect of rTMS on patients with epilepsy in the fourth section. Although conflicting results have been reported, growing evidence supports slow frequency rTMS is effective in reducing seizure frequency and /or decreasing the EEG epileptiform abnormalities. Some problems will be also referred to in this section.

The safety issue of rTMS is another topic for this chapter. Currently available data showed that TMS is a safe technique, both in normal subjects and neurologically impaired patients. No long-lasting effects on cognitive, motor or sensory functions have been reported. As far as seizures are concerned, only 6 seizures have been elicited by rTMS in 6 non-epileptic individuals by the end of 1996. Although high-frequency rTMS may induce accidental seizures in normal subjects and epileptics, slow frequency rTMS has not been shown to induce seizures in patients with epilepsy. The safety issue of TMS will address in a separate paragraph.

The final section will discuss the prospects of rTMS. As a noninvasive, easily applied and safe technology, rTMS may be an effective adjunctive treatment for patients with refractory epilepsy, and may provide a valuable insight into pathophysiological mechanisms underlying epileptic processes and AED-induced changes of the excitability of cortical networks. In addition, rTMS changes induced by different AEDs could be used as a neurophysiological index to optimize the treatment in a given patient. More work is needed to do before wide use of rTMS in the epileptic field.

2. TMS techniques and measures of motor excitability

TMS has mainly three categories: single-pulse TMS (sTMS), paired-pulse TMS (pTMS) and repetitive TMS (rTMS). Single-pulse TMS refers to stimulation with a conventional stimulator, which delivers pulses no faster than 1 Hz. It can be used to obtain motor threshold (MT) and cortical silent period (CSP). Paired-pulse TMS techniques involve a conditioning pulse followed by a test stimulus, which are delivered to the same scalp position through a single coil. It has been used to study intracortical inhibition and facilitation. Repetitive TMS indicates trains of regularly repeated magnetic pulses delivered to a single scalp site (Wassermann, 1998). It can also stimulate neurons in unresponsive period, thus preferentially activating tangentially-oriented connecting neurons, which produce excitatory postsynaptic potentials and disrupt the balance between cortical excitability and inhibition.

The parameters used to study experimentally and clinically mainly include motor evoked potential (MEP), motor threshold (MT), cortical silent period (CSP), intracortical inhibition (ICI), and intracortical facilitation (ICF). MEP reflects the excitability of the whole corticospinal system. MEP size increases with contraction of the target muscle, and increases with stimulus intensity in a sigmoid manner. The part of the MEP intensity curve close to MT is determined by the excitability of low-threshold corticospinal neurons, and the high-intensity part of the MEP intensity curve reflects the excitability of high-threshold neurons (Devanne et al., 2002). MEP size may be modulated by inputs to motor cortex from the periphery or other parts of the brain. MEP is a reliable tool to monitor focal cortical excitability.

MT is the minimum stimulus intensity needed to elicit a small motor response in the target muscle, in at least half of 10 consecutive trials. MT can be determined at rest (RMT) or

during slight isometric muscle activation (AMT). RMT is determined by the excitability of corticocortical axons and the excitability of synaptic contacts between these axons and corticospinal neurons and between corticospinal neurons and their target motoneurons in the spinal cord. Whereas, AMT is mainly determined by the excitability of corticocortical axons and therefore mainly reflects membrane-related excitability and correlates with ion channels(Hallett ,2007).

CSP refers to a period of silence in the electromyographic pattern of a voluntarily contracted target muscle. Its size reflects the length of intracortical inhibition. The early part of the CSP reflects the inhibitory effect at spinal level, and the late part reflects inhibition at the level of the motor cortex. It is conceived that the late part of the CSP is determined by long-lasting cortical inhibition mediated through the γ -aminobutyric acid type B receptor(Hallett,2007; Ziemann et al.,2006).

Intracortical inhibition (ICI) and intracortical facilitation (ICF) are two parameters provided by pTMS, which reflect neuronal inhibition and excitability, respectively. It is thought that paired-pulse measures reflect mainly synaptic excitability of various inhibitory and excitatory neuronal circuits at the level of the motor cortex. This synaptic excitability is controlled mainly by neurotransmission through the GABA and N-methyl-D-aspartate (NMDA) receptors. Short-interval intracortical inhibition (SICI) and long-interval intracortical inhibition (LICI) underlie separate mechanisms and may reflect inhibition mediated through the GABA_A and GABA_B receptors, respectively(Ziemann et al.,2006; Sanger et al 2001).

3. Possible antiepileptic mechanisms of rTMS

The pathogenic mechanism of epilepsy is very complicated. It may involve several aspects, including the imbalance of cortically excitatory and inhibitory activities, disturbance of neurotransmitter, abnormality of the structure and/or function of ion channels, decrease of endogenous neuropeptides, and metabolic disorder in the brain. Whether rTMS affects epileptic seizure through one or more abovementioned factors is almost unknown. Some pilot researches in this aspect are summarized as follows.

3.1 Electrophysiologic mechanism

Some clinical studies found that RMT and intracortical inhibition in untreated epileptic patients decreased remarkably, and the more the RMT decreased, the more frequently the seizure attacked(Kotova &Vorob'eva,2007). Inghilleri et al reported that CSP in the epileptogenic hemisphere was much shorter than in the contralateral hemisphere(Inghilleri et al.,1998). Cincotta and coworkers found CSP got much longer after receiving 30 minutes, 0.3 Hz rTMS(Cincotta et al.,2003). These studies suggested, for one thing, that imbalance between excitatory and inhibitory neurons existed unquestionably, for another, that rTMS may strengthen the inhibitory effect and therefore regain a new balance, thus leading the seizure decrease or remission. In our recent study, we found that the rats injected intraperitoneally with epileptogenic dose of pilocarpine immediately followed by 40-minute rTMS treatment (0.5 Hz, 95% RMT) had much milder seizure and lower rate of SE development in 90-minute follow-up period, compared with rats without rTMS treatment (not published). This result makes us reasonably infer that the quick antiepileptic effect of rTMS more likely resulted from its direct modulation on the activity of excitatory and inhibitory neurons in the cortex than from its indirect effect by inducing the enhancement of

endogenous inhibition. Therefore, Modulating the excitability and inhibition in the cortical neurons may be one of the antiepileptic mechanisms of rTMS.

3.2 Neurotransmitter mechanisms

Neurotransmitters in the brain functionally include excitatory neurotransmitters and inhibitory neurotransmitters, which represent by glutamate and γ -aminobutyric acid, respectively. In normal state, the excitatory neurotransmitters and the inhibitory neurotransmitters maintain a balance. Once the activity of excitatory neurotransmitters becomes hyperactive, or the activity of inhibitory neurotransmitters remarkably decreases, a seizure may occur. N-methyl-D-aspartate (NMDA) receptor-1 is one of the most important glutamate receptors and also the main mediator of calcium ion channel and epileptogenic factor. GAD65 is the key enzyme in the process of GABA synthesis and it has the quality of high specificity and stability. Therefore, NMDAR1 and GAD65 usually act as two marks to evaluate the levels of glutamate and GABA in the brain, respectively.

Zhang et al in the rat pilocarpine seizure model found that the rats pretreated with two-week rTMS (administered at 0.5 Hz, 95%MT) had increased expression of GAD65 and decreased expression of NMDAR1 in the hippocampal CA1, which investigated at 90 minutes after injecting pilocarpine (Zhang et al., 2008). Michael et al in the study of healthy volunteers adopted proton magnetic resonance spectroscopy (MRS) to investigate the effects of high frequency rTMS on brain metabolism. They found that the content of glutamate had a pronounced change not only around the stimulating zone but also the remote areas (ipsilateral and contralateral to the stimulus site) (Michael et al., 2003). Zangen et al in the experimental study also found that the glutamate in the stimulated left prefrontal cortex increased significantly after high frequency rTMS (Zangen & Hyodo, 2002). These results suggested that low-frequency and high-frequency rTMS may have different effects on excitatory and inhibitory neurotransmitters or their receptors. The antiepileptic effect of low-frequency rTMS might be related to the upregulation of GAD65 expression and downregulation of NMDAR1 in the hippocampus.

Clinical study on patients with epilepsy revealed a dynamic change for ICI and ICF (Turazzini et al., 2004). The CSP had no longer linear relation with the stimulus intensity when the patients with focal epilepsy were administered at a certain stimulus intensity (Cicineli et al., 2000). Some researchers reported that the changes of GABA receptors are proportional to the changes of ICI, whereas the changes of glutamate receptors are proportional to the changes of ICF (Sanger et al., 2001; Hamer et al., 2005; Issac, 2001). In addition, some studies demonstrated that the late part of CSP was determined by LICI, which was mediated through GABA_B receptors.

3.3 Ion channel structure and function mechanisms

It is clear that seizures are linked to membrane potentials, ionic fluxes, and action potential generation. In neurons, action potential generation results primarily from changes in the membrane permeability to four ions: sodium, chloride, calcium, and potassium. These ions enter and exit neurons by way of voltage-dependent channels. Once the ion channel functions abnormally, the ionic concentrations intracellularly and extracellularly will probably change and result in ictal discharges or seizures.

Genetic study has shown that the mutation of the gene coping KCNQ2 and KCNQ3 leads to benign neonatal familial convulsions. But whether or not rTMS is able to affect the gene of

ion channels is unknown. Theodore found that rTMS was able to change the flow velocity and distribution of sodium and calcium, and therefore affect membrane permeability (Theodore, 2003). Our most recent study, pretreating rats for two weeks with 0.5 Hz rTMS before making pilocarpine-induced model, showed that rTMS can transiently downregulate the expression of sodium channel subunit SCN1A, but upregulate the expression of potassium channel subunit Kcal 1.1 in the hippocampus, and the latter effect maintained at least six weeks (not published). These results suggest that by changing the expression of ion channel genes may be another antiepileptic mechanism of rTMS.

3.4 Protective mechanism

It is well known that the over expression of Bcl-2 can inhibit neuron apoptosis resulted from multiple factors, such as overload of calcium, oxygen free radicals, glutamate and deficiency of neural growth factors (Zhong et al., 1993). This may be one of the self rescue mechanisms. Ke et al found that one-week daily rTMS before making rat pilocarpine seizure model can lead to Bcl-2 upregulation in the hippocampus CA1 (Ke et al., 2010). Song et al in a similar study also found that rTMS can inhibit neuronal apoptosis, lessen necrosis resulted from apoptosis in the temporal tissue (Song & Tian, 2004). MRS study showed that the hippocampal content of choline-containing compounds (CHO) in the rTMS treated chronic temporal lobe epilepsy (TLE) rats was much lower than that in the rTMS untreated chronic TLE rats. This implied that rTMS delayed or alleviated gliosis in the rTMS treated TLE rats (Song & Tian, 2005). Post et al. in their study found that rTMS resulted in a significant increase of secreted amyloid precursor protein (SAPP) in the hippocampal neurons, which is a kind of spanning membrane glucoprotein, similar to cell surface receptor in structure (Post et al., 1999). SAPP has multiple effects, including protecting neurons, promoting cell survival, and stimulating neuronal axon growing. The above-mentioned study suggested that rTMS may have the ability to protect against the insult from TLE. This effect may be its another mechanism in counteracting epilepsy, especially chronic epilepsy.

3.5 Other mechanisms

3.5.1 Metabolism

Some studies showed that both high-frequency rTMS and low-frequency rTMS can change the brain metabolism, not only in the stimulating areas, but also in the remote zones (Michael et al., 2003; Song & Tian, 2005; McCann et al., 1998). In a clinical trial, Speer adopted high-frequency rTMS (20 Hz) and low-frequency rTMS (1 Hz) to treat patients with depression, and used positive emission tomography (PET) to measure the brain metabolism. They found that high-frequency rTMS had a better outcome in patients with hypermetabolisms, but low-frequency rTMS had a better outcome in patients with hypometabolisms (Speer et al., 2009). This result suggested that high-frequency rTMS and low-frequency rTMS may affect the brain metabolisms in opposite way: low-frequency rTMS reduces metabolism, high-frequency rTMS enhances metabolism. It is therefore reasonably deduced that the antiepileptic effect of low-frequency rTMS may be related to its ability to reduce the brain metabolism.

3.5.2 Regional cerebral blood flow (rCBF)

Both high-frequency rTMS and low-frequency rTMS can affect the change of regional cerebral blood flow in the stimulated areas. Graff-Guerrero et al described two patients with

epilepsia partialis continua (Graff-Guerrero et al., 2004). They investigated these two patients by single photon emission computed tomography (SPECT) before and after rTMS treatment. They found that both have hyperperfusion in the epileptogenic zones before rTMS. But this phenomenon abolished after rTMS treatment. Therefore, modulation of rCBF around the epileptogenic zone may contribute to the control of seizures.

3.5.3 Endogenous antiepileptic mechanism

Anschel et al did an interesting experiment. In this study, they administered a patient with depression with rTMS for 8 consecutive days, then they injected the cerebrospinal flow into the lateral ventricle of rats. They surprisingly found that the flurothyl-kindling effect was significantly mitigated (Anschel et al, 2003). This result suggested that the CSF of the rTMS treated patient must contain some endogenous antiepileptic substance. Therefore, it reasonably infers that rTMS may have the ability to stimulate the release of some endogenous antiepileptic substances.

4. Effects of AEDs on TMS parameters and their clinical values

4.1 TMS parameters versus AEDs and their possible mechanisms

Extant data show that the effects of different antiepileptic drugs on TMS parameters are variable. It has been found that the MT is increased after acute administration of the voltage-dependent sodium channel blockers carbamazepine (CBZ), lamotrigine (LTG), and phenytoin (PHT) (Boroojerdi et al., 2001), and the maximum MT was observed at the plasma peak time in normal subjects (Ziemann et al., 1996). These findings were also reported in epileptic patients. However, many patients were under chronic AED treatment at the time of TMS testing. This suggests that the increased MT may result from the threshold increasing effect of AEDs in epileptic patients. This view was directly supported by the demonstration that untreated groups of patients with idiopathic generalized epilepsy (IGE) (Reutens et al., 1993) or benign epilepsy with centrotemporal spikes (Nezu et al., 1997) had reduced or normal RMT values compared with healthy controls. However, RMT in the patient groups increased significantly above normal level when remeasured after the commencement of treatment with valproic acid (Reutens et al., 1993; Nezu et al., 1997). In a study on temporal lobe epilepsy patients, RMT significantly increased with the number of AEDs taken by the patients (Hufnagel et al., 1990). In one subgroup of this study, RMT dropped significantly after tapering AED treatment (Hufnagel et al., 1990). On the contrary, some studies found RMT is increased in untreated IGE patients (Gianelli et al., 1994). This elevation of MT may reflect cortical dysfunction after the seizure or is likely a protective mechanism against spread or recurrence of seizures. For these reasons, some researchers applied TMS to evaluate the antiepileptic effects of PHT and CBZ monotherapy. They found a higher MT and a lower MEP in the PHT group than those in CBZ group, which implies PHT may have stronger inhibitory effect on cortical excitability compared with CBZ (Goyal et al., 2004).

In contrast to ion channel blocker intake, a single dose of drugs enhancing γ -aminobutyric acid (GABA)-mediated inhibitory neurotransmission, such as baclofen, diazepam, ethanol, lorazepam, tiagabine, and vigabatrin, does not modify the MT in healthy subjects (Tassinari, 2003), but may change the cortical silent period duration (CSP), intracortical facilitation (ICF), and intracortical inhibition (ICI) (Tassinari, 2003). Reis et al found that topiramate, which can enhance the GABA-mediated inhibitory effect and counteract the toxic effect of excitatory amino acid, is able to elevate ICI but does not affect MT and CSP (Reis et al., 2002).

Another study showed that gabapentin had no effect on MT, but reduced the ICF, increased ICI and CSP(Rizzo et al.,2001). This suggests that gabapentin may enhance the GABAergic neurotransmission. In a study on levetiracetam, MT significantly increased, but CSP, ICI, and ICF unchanged(Reis et al.,2004). This implies that levetiracetam may have block effect on sodium channel.

In summary, the relationship between TMS parameters and AEDs is complicated. Ziemann reviewed the literatures and concluded that ion channel blocker AEDs can elevate MT, but have no effect on CSP, ICI and ICF, whereas, enhancing GABAergic AEDs, such as lorazepam, diazepam, vigabatrin, and tiagabine, mainly affect CSP, SICI, ICF, SICF, but have no effect on MT (see table 1)(Ziemann, 2004) MEP can be used as one of the most sensitive indexes in investigating the effects of AEDs.

drug	Mode of action	TMS variables					
		MT	MEP	CSP	SICI	ICF	SICF
CBZ	Na ⁺	1+	0	1+	0/0	0/1-	0
PHT	Na ⁺	2+	0/0	0/0			
LTG	Na ⁺	3+	1-	0	0/0	0/0	0
VPA	Na ⁺ /GABA	0		0	0	0	
LZP	GABA	0/0/0	2-	1+	0/2+	0/1-	1-
DZP	GABA	0/0	1-/0	0/1-	0/1+	1-	1-
TP	GABA	0	1-	0			
VGB	GABA	0	0/0	0/0	0	1-	1-
TGB	GABA	0	0	1+	1-	1+	

carbamazepine: CBZ, phenytoin: PHT, lamotrigine: LTG, valproate: VPA, lorazepam: LZP, diazepam: DZP, thiopental: TP, vigabatrin: VGB, tiagabine: TGB; no clear change: 0, increase: 1+, clear increase: 2+, significant increase: 3+, decrease: 1-, clear decrease: 2-.

Table 1. Effects of antiepileptic drugs on TMS variables

Sohn et al(Sohn et al.,2004) summarized corresponding MEP changes after using sodium channel blocker LTG and GABA receptor agonist thiopental and lorazepam, and transferred these changes into curves. They found that both of the sodium channel blocker and GABA receptor agonist made the curves shift down.

The early part of the CSP is easily affected by spinal inhibitory mechanisms, whereas the late part most probably reflects inhibition specifically at the level of the motor cortex (Hallett,2007; Ziemann et al.,2006). It is thought that this late part of the CSP is determined by long-lasting cortical inhibition (LICI) mediated through the GABA type B receptor. Interestingly, AEDs (CBZ, LZP) with different modes of action may produce similar CSP prolongation, whereas those with the same modes of action (LZP, DZP) may result in different CSP changes, which are shown in table 1(Sohn et al.,2004; Sundaresan et al., 2007). These inconsistent findings suggest further study is needed to clarify the relationship between TMS variables and AEDs.

It is thought that LICI may reflect the long-last inhibition mediated by GABA_B receptors. Therefore, the pronounced enhancement of LICI may be the result of the potentiated neurotransmission mediated through the postsynaptic GABA_B receptors(Werhahn et

al.,1999). Short-interval intracortical inhibition (SICI) may reflect the inhibition mediated through GABA_A receptors. Most of the GABA_A receptor agonists, such as LZIP, DZIP may increase SICI. The duration of SICI correlates with that of the inhibitory postsynaptic potential which is mediated through GABA_A receptors. Combined with inter-stimulus intervals, SICI can be used in ICF evaluation. This suggests that the excitatory interneurons, which mediate ICF, are controlled by inhibitory interneurons, and this influences are dose-dependent(Reis et al.,2004; Ye&Zhang,2000). AEDs of sodium channel blockers exert no clear effect on SICI, as opposed to ICF.

4.2 The relation between TMS variables and the plasma concentrations of AEDs

The relation between RMT and the plasma concentration of AEDs shows a sigmoid(Della Paschoa et al.,2000). A study on 16 healthy subjects taking LTG showed a linear relation between the MT and the LTG plasma concentration (in the range of 430ng to 2500ng/ml)(Tergau et al.,2003). Cantello et al demonstrated that the MT and the plasma concentration, in a study of 15 patients with symptomatic epilepsy taking VPA, had a positive linear relation, whereas a sigmoid relation in 18 healthy subjects (Cantello et al., 2006). Werhahn et al reported that the dose of TGB had a positive linear relation with CSP and ICF. Although TGB can affect SICI, the relation between the dose and SICI is unclear(Werhahn et al.,1999). In a study of CBZ, Turazzini administered 10 patients with symptomatic epilepsy with daily 200mg dose of CBZ, and with an increment of 200mg every other day, then maintained at 800mg daily. They found a linear relation between RMT increases and the serum concentration of CBZ before a stable level after they monitored the changes of serum CBZ and TMS parameters at a certain interval in 2 months(Turazzini et al.,2004). They also found in this study that MEP, CSP, SICI and ICF had no pronounced changes(Turazzini et al.,2004). Lee et al demonstrated a similar effect of CBZ and LTG on MT in the 5-week duration of observation in 20 volunteers, but this was mainly seen at the late stage, and can be explained as follow-up effect(Lee et al.,2005).

4.3 Prospect of TMS in the study of AEDS

TMS variables may be helpful to investigate the unknown mechanisms of some AEDs. Although single- and paired-pulse TMS parameters show high variability across subjects, their interside and longitudinal intraindividual variability is lower. Therefore, repeated recordings in the same subjects appear to be a sensitive tool to disclose minor AED-induced changes(Tassinari et al,2003). Furthermore, the threshold intensity varied with the changes of AED dose, or had a positive linear relation with serum levels of AEDs. This suggests that monitoring the change of TMS threshold intensity, just as monitoring the plasma drug concentration and electroencephalography (EEG), could be acted as a tool to guide optimum use of AEDs. In addition, according to the correlation of drug serum concentration and TMS parameters, TMS might be used as an adjunctive means to monitor brain cortical excitability when studying the pharmacodynamics of AEDs. This implies that TMS may be used to evaluate the newly developed antiepileptic drugs.

5. The therapeutic effect of rTMS on patients with epilepsy

5.1 Experimental animal study

A series of animal studies have shown that low-frequency rTMS has antiepileptic effect, and this effect is frequency dependent. Akamatsu et al demonstrated that rTMS of 1000 pulses at

0.5 Hz led to a prolonged latency for seizure development and a lower ratio of status epilepticus after an intraperitoneal injection of pentylenetetrazol in Wistar rats (Akamatsu et al., 2001). Godlevsky and coworkers (Godlevsky et al., 2006) experimented on male WAG/Rij rats with rTMS of 3 impulses at 0.5 Hz and combined recording of electrocorticograms. They found that such stimulation engendered a reduction of spike-wave discharge bursts duration, which was most pronounced in 30 minutes from the moment of cessation of stimulation, but bursts of spike-wave discharges restored up to pre-stimulative level in 90-150 minutes. This result suggested that rTMS possessed an ability to produce short-time suppression of bursts of spike-wave discharges in WAG/Rij rats, a gene model of absence seizure. Rotenberg et al (Rotenberg et al., 2008) tested the anticonvulsive potential of rTMS with different stimulation frequency in the rat kainic acid seizure model. They divided 21 rats into three groups in which individual seizures were treated with rTMS trains at one of three frequencies: 0.25, 0.5 or 0.75 Hz. The rTMS treatments were guided by simultaneous EEG monitoring, that is, rTMS treatment (active rTMS, sham rTMS, or untreat) was administered only when consecutive seizures occurred. They found that KA-induced seizures were abbreviated by 0.75 Hz and 0.5 Hz active EEG-guided rTMS, but neither active 0.25 Hz rTMS nor the control conditions affected seizure duration. This result indicated that rTMS has therapeutic potential, but is frequency dependent. Ke Sha et al (Ke et al., 2010), as well as Huang Min et al (Huang et al., 2009), also investigated the efficacy of a range of rTMS frequencies, but in another model: pilocarpine seizure model. They divided rats into different groups according to the rTMS frequency delivered at the treatment, and pretreated each rat with corresponding frequency's rTMS for consecutive two weeks. After finished the pretreatment, each rat was given an intraperitoneal injection of pilocarpine. They demonstrated that pretreatment with TMS at 0.3, 0.5, 0.8, and 1.0 Hz all led to a longer latency of seizure onset, but 0.5 Hz and 0.8 Hz rTMS treatment engendered the longest latency for seizure development and conspicuous anticonvulsive effects.

5.2 Clinical study

Tergau and coworkers (Tergau et al., 1999) first reported the treatment of rTMS on patients with epilepsy in 1999. In their trial, nine patients with medically refractory frontal epilepsy were enrolled. All patients had more than seven focal or secondarily generalized seizures per week in the 6 months before rTMS treatment. After rTMS, which was delivered over the vertex with two trains of 500 pulses at a frequency of 0.33 Hz on 5 consecutive days, weekly seizure frequency dropped significantly from an average of 10.3 to 5.8. Seizures did not occur during rTMS. After 6 to 8 weeks, seizure frequency returned to baseline level. Since then, a lot of clinical reports were followed (see Table 2-4). Fregni et al (Fregni et al., 2006) randomly divided 21 patients with refractory epilepsy into active rTMS group and sham rTMS group. rTMS was administered with 5 trains of 1200 pulses and an intensity of 70% rMT at frequency of 1 Hz on 5 consecutive days. They noticed that, compared with sham rTMS group, the seizure frequency and the number of spikes in ictal EEG were significantly reduced, and their cognition was also improved after rTMS. This effect lasted at least 2 months. Santiago-Rodriguez et al (Santiago-Rodriguez et al., 2008) evaluated the number of seizures and interictal epileptiform discharges (IEDs) in 12 patients with focal neocortical epilepsy before, during and after rTMS. rTMS was administered with 900 pulses at 0.5 Hz for 2 consecutive weeks at 120% rMT. They found that the mean seizure frequency decreased from 2.25 per week (basal period) to 0.66 per week (intervention period), a 71%

reduction ($p=0.0036$). In the 8-week follow-up period the mean seizure frequency was 1.14 per week, which corresponds to a 50% reduction compared with basal period. Moreover, EEG analysis displayed IED frequency was also reduced; it decreased from 11.9 (baseline) to 9.3 (during 2 weeks of rTMS) with a further reduction to 8.2 in the follow-up period. These differences on EEG however were not significant ($p=0.190$). Joo et al (Joo et al., 2007) investigated the antiepileptic effect of low-frequency rTMS in 35 patients with intractable epilepsy. Patients were divided into a focal stimulation group with a localized epileptic focus, or a non-focal stimulation group with a non-localized or multifocal epileptic focus. Each group was then randomly subdivided into 3000 pulses and 1500 pulses subgroups. rTMS was administered at 0.5 Hz for 5 consecutive days at 100% of rMT. Weekly seizure frequency were determined for 8 weeks before and after rTMS, and the number of interictal spikes before (1st day) and after rTMS (5th days) were also compared. They demonstrated that interictal spikes significantly decreased (-54.9%, $p=0.012$) and even totally disappeared in 6 patients after rTMS. Although mean weekly seizure frequency was non-significantly decreased after rTMS, longer stimulation subgroups (3000pulses, -23.0%) tended to have fewer seizures than shorter stimulation subgroups (1500pulses, -3.0%), without statistical significance. They also found TMS stimulation site and structural brain lesions did not influence seizure outcome. Wang et al (Wang et al., 2008) randomly divided 30 patients with temporal lobe epilepsy, which was determined with dipole source, into drug group and rTMS group, each group with 15 patients. Drug group were given antiepileptic drug only (AED) (carbamazepine, 600-800mg daily, three times a day); rTMS group were given rTMS treatment as well as AED (carbamazepine, 600-800mg daily, three times a day). rTMS was administered using Dantec Maglite-r25 with 500 pulses at 1 Hz for consecutive seven days at intensity of 90% MT. After 7 days of rTMS treatment, both groups continued to take AED. They found that seizure frequency had no significant difference between rTMS group and drug group. However, interictal spikes decreased significantly in rTMS group compared with drug group on the 30th day after rTMS.

Regrettably, the results of rTMS in the treatment of epilepsy almost exclusively came from interictal epileptic patients. There are very few studies based on ongoing seizures. Nevertheless, Rotenberg and coworkers' study is encouraging (Rotenberg et al., 2009). In their study, seven patients with *epilepsia partialis continua* (EPC) of mixed etiologies were treated with rTMS over the seizure. rTMS was delivered in high-frequency (20-100 Hz) bursts or as prolonged low-frequency (1 Hz) trains. The result is that rTMS led to a brief (20-30 min) pause in seizures in three of seven patients and a lasting (no less than one days) pause in two of seven. Seizures were not exacerbated by rTMS in any patient. Only mild side effects including transient head and limb pain, and limb stiffening during high-frequency rTMS train occurred.

Above-mentioned studies both clinically and experimentally indicate that rTMS is effective and safe in the treatment of epilepsy. It can not only decrease seizure frequency, but also reduce spikes firing, even terminate ongoing seizures. Some researchers have recommended rTMS to be a method to treat refractory epilepsy. Nevertheless, it will be a long way before rTMS really puts to clinical practice. The reason is that current data about effectiveness of rTMS mainly resulted from small size trials, even case report, lack of convincingly large size and randomly controlled trials, and that the parameters (including stimulus frequency, intensity, number of stimuli, train duration, intertrain interval, coil type, and stimulation sites) used in rTMS studies or treatment are different among researchers (see table 5). This may be why some incongruent, even conflicting results occurred.

First author and publish time	Subjects	Epilepsy syndorme	Seizure frequency pre-TMS	Seizure frequency Post-TMS	Epileptiform Discharges Post-TMS
Menkes, 2000	1	ETLE	37/month	Reduction	Reduction
Cantello, 2002	1	Primary generalized	NR	No reduction	Reduction
Rossi, 2004	1	EPC	EPC	Reduction	Reduction
Graff-Guerrero 2004	2	EPC	EPC	Reduction in one of two patients	Reduction
Misawa,2005	1	EPC	EPC	Reduction for two month	NR
Mecarelli, 2006	1	Focal	NR	Reduction	No Reduction
Brighina, 2006	9	Focal=3 Multifocal=6	NR	Reduction only during protocol	NR

ETLE=extra temporal lobe epilepsy; MTLE= mesial temporal lobe epilepsy; TLE=temporal lobe epilepsy; NR=not reported; EPC= Epilepsia partialis continua.

Table 2. Impact of rTMS on epilepsy(Case report study)

First author and publish time	Subjects	Epilepsy syndorme	Seizure frequency pre-TMS	Seizure frequency post-TMS	Epileptiform Discharges Post-TMS
Tergau, 1999	9	TLE=2 ETLE=7	10.3±6.6/w	5.8±6.4/w	NR
Daniele, 2003	4	Frontal=2 Multifocal=2	19/month(focal), 36/month(multifocal)	Reduction(in patients with single focus)	NR
Brasil-Neto, 2004	5	TLE=2 ETLE=3	1.4±0.09/d	Reduction	NR
Fregni 2005	8	TLE=3 Multifocal=4 ETLE=1	3-6.2/w	Reduction for 1 month	Reduction for 1 month
Kinoshita, 2005	7	Focal	16.5±5.2/w	Reduction	NR
Santiago-Rodriguez, 2008	12	Focal	2.25/w	Reduction	No reduction
Rotenberg 2009	7	EPC	EPC	Reduction	NR
Wei Sun 2011	17	Refractory partial	14.09±16.55/w	Reduction	No reduction

d=day;w=week

Table 3. Impact of rTMS on epilepsy(Open-label study)

First author and publish time	Subjects	Epilepsy syndorme	Seizure frequency pre-TMS	Seizure frequency post-TMS	Epileptiform Discharges post-TMS
Theodore 2002	12	Focal	3.4±1.2/w	No reduction	NR
Tergau 2003	17	MTLE/ETLE/ Multifocal/Generalized	NR	Reduction (only0.33 HZ)	NR
Fregni 2006	12	Focal	13.6±10.1/28d	Reduction (at least two month)	Reduction (at least two month)
Joo 2007	35	Focal/Multifocal/Non-localized	9.9±10.1/w (NF group) 7±9.6/w (F group)	Trend for reduction	Reduction
Cantello, 2007	43	Focal	9.1±2.2/w	No reduction	Reduction
Wang 2008	15	TLE	1.9±0.4/w	No reduction	Reduction

Table 4. Impact of rTMS on epilepsy (Double-blinded and sham-controlled study)

6. The safety issue of rTMS

Although extant researches have shown that rTMS is a promising tool in treating epilepsy, its safety and tolerability have been the focus of concerns. rTMS does have the potential for short-term adverse side effects such as headache, tinnitus, insomnia, discomfort at the site of stimulation, but its long-term adverse side effects are unknown. Studies in normal human subjects have shown that rTMS had no long-term adverse effects on blood pressure, heart rate, balance, gait, sensory function, motor function, memory and cognition(Pascual-Leone et al.,1993; Hufnagel et al.,1993), and found no changes in electroencephalogram (EEG), electrocardiogram (ECG), serum hormone(Jahanshahi et al.,1997). Studies of the anatomical effects of rTMS have shown that conventional and diffusion-weighted magnetic resonance imaging are normal following long duration, high-intensity rTMS that exceeded safety guidelines, and MRI is normal following rTMS used for 2 weeks in treating depression (Anand S&Hotson J,2002). Moreover, no pathological changes are seen in resected temporal lobe tissue following approximately 2000 pulses(Gates et al.,1992). In addition, metabolic study showed that proton magnetic resonance spectroscopy (MRS) revealed no significant alterations of N-acetyl-aspartate, creatine and phosphocreatine, choline-containing compounds, myo-inositol, glucose and lactate, and post mortem histology revealed no changes in microglial and astrocytic activation following rTMS regimen of 1000 stimuli used for 5 consecutive days at 1 Hz(Liebetanz et al.,2003).

Another safety issue of rTMS is its effect on cognition(Anand S&Hotson J,2002). Most safety studies have not reported adverse long-term effects in cognitive function in subjects receiving rTMS. One study found degradation in short term verbal memory immediately following rTMS, but the effect did not persist following the study and was attributed to the short inter-train intervals that were also cause seizures in normal subjects. Performance on

standard neuropsychological tests is not adversely affected by rTMS sessions; instead, verbal memory tends to improve and motor reaction time tends to decrease.

First author and publish time	Frequency (Hz)	Intensity	Stimuli	Schedule	Coil form	Position
Tergau, 1999	0.33	100%rMT	500/train	5trains/d* 5d	Round	Vertex
Menkes, 2000	0.5	95%rMT	20/train	5trains/ d*bw*3m	Round	EGF
Cantello, 2002	5	120%MT	NR	Onset of spikes	NR	NR
Theodore, 2002	1	120%MT	900/train	2train/d*7d	Figure-of-eight	EGF
Tergau, 2003	0.33, 1	below MT	1000/train	1train/d*5d	Round	Vertex
Daniele, 2003	0.5	90%MT	100/train	bw*4w,	Figure-of-eight	EGF/ vertex
Rossi, 2004	1	90%rMT	900	Single session	Figure-of-eight	EGF
Brasil-Neto, 2004	0.3	95%MT	20/train	5trains/d*BW*3 m	Round	Vertex
Graff-Guerrero 2004	20	50%, 128%MT	40/train	15days	Figure-of-eight	EGF
Fregni 2005	0.5	65%MSO	600	Single session	Figure-of-eight	EGF/ vertex
Kinoshita 2005	0.9	90%rMT	810/train	2trains/d*5d*/ w*2w	Round	FCz, PCz
Fregni 2006	1	70%MSO	1200/train	1train/d* 5 d	Figure-of-eight	EGF/ vertex
Mecarelli 2006	0.33	100%rMT	500/train	2train/d *5 d	Round	Vertex
Brighina 2006	5	100%rMT	100/train	20d	Figure-of-eight	Near inion
Joo, 2007	0.5	100%MT	3000/train / 1500/train	1train/d* 5 d	Round	Vertex/ temporal
Cantello, 2007	0.3	100%MT/ 65%MSO	500/train	2trains/d*5 d	Round	Vertex
Santiago- Rodriguez, 2008	0.5	120%rMT	900/train	1train/d*2 w	Figure-of-eight	EGF
Wang, 2008	1	90%MT	900/d	7 d	Figure-of-eight	EGF
Rotenberg, 2009	100, 20, 1	100%MT	NR	Difference	Figure-of-eight	EGF

bw=biweek; m=month; MSO=maximum stimulator output intensity; EGF=epileptogenic focus.

Table 5. Brain stimulation parameters

The third safety issue of rTMS is its effect on endocrine system(Anand&Hotson,2002). One study found no change in hormonal levels in humans following rTMS, but a decrease in

serum prolactin levels, which is opposite the effect seen after a seizure, and an increase in thyroid-stimulating hormone level, which accompanied an improved mood, were found following rTMS.

The greatest concern with rTMS is the induction of seizures. Even in normal healthy subjects, prolonged, high intensity, rTMS with rate of 10-25 Hz can produce partial seizure with or without secondary generalization. After analyzing thousands of rTMS treated patients, Rosa et al (Rosa et al., 2004) think TMS is safety. They found only 6 patients had an occasional seizure, and the risk factors of seizures elicited by TMS included brain tumor, stroke, inflammation, severe trauma, increased cranial pressure, idiopathic epilepsy, uncontrolled epilepsy, taking some drugs which reduce the threshold of seizures such as tricyclic antidepressants, excessive drinking, and use of stimulant drugs.

The guidelines released by National Healthy Institute of America in 1998 believed that rTMS was relative contraindication to patients with epilepsy, but safe on the condition of strictly controlling stimulating parameters and regular operation (Wassermann, 1998). Schrader et al (Schrader et al., 2004) concluded from the analysis of some studies that the peak rate of seizure occurrence related to TMS was 2.8 percent in sTMS, 3.6 percent in pTMS, and the modes of onset were similar to their typical attack; no long-term adverse effects were found and the increased seizure frequency could not exclude the possibilities of intractable epilepsy, decreased use of medication, improper operation and strongly stimulating intensity. Studies of safety evaluation of the combinations of parameters (0.5 Hz, 50 pulses; 8 Hz, 1000 pulses; 20 Hz, 1500 pulses; 25 Hz, 1200 pulses) showed that rTMS delivered in any combination of parameters was safe (Liebetanz et al., 2003; Frye et al., 2008; Post et al., 1999). Bae EH et al (Bae et al., 2007) performed an English-language literature search, and reviewed all studies published from January 1990 to February 2007 in which patients with epilepsy were treated with rTMS. They found that the adverse events attributed to rTMS were generally mild and occurred in 17.1% of subjects; headache was most common, occurring in 9.6%; seizures occurred in 4 patients (1.4%); all but one case were the patients' typical seizures with respect to duration and semiology, and were associated with low-frequency rTMS; a single case had atypical seizure appearing to arise from the region of stimulation during high-frequency rTMS; no rTMS-related episodes of status epilepticus were reported. They concluded that rTMS appeared to be nearly as safe in patients with epilepsy as in nonepileptic individuals.

Based on the consideration of safety, current studies support to use slow-frequency rTMS for the purpose of treatment in epilepsy. As for selecting of parameters, which include stimulus frequency, intensity, intertrain interval, and stimulus site, it should depend on individuals and comply with some norms. Besides, the accurate localization of the stimulus site is also the important part of safety study (Hoffman et al., 2005).

Wassermann (1998) provided a comprehensive report of new guidelines based on the deliberations of an "International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, Jun 5-7, 1996." He reiterated three requirements central to research on human subjects, namely, the need for informed consent, the requirements that the potential benefit of the research outweighs the risk as independently assessed by an investigational review board, and the need "for equal distributions of the burdens and the benefits of the research" The research should not be conducted on categories of vulnerable patients or subjects who are likely to bear the burden of the research without the potential for benefit.

Wassermann suggested three types of studies appropriate for rTMS. First are studies where there are reasons to expect direct benefit to patients, such as the treatment of major

depression. Second are studies of the pathophysiology of a brain disorder that may add information leading to new therapeutic strategies. These studies would include the participation of normal subjects as controls. Third are studies in normal subjects or patients that are expected to produce original and important observations about brain function that can not be obtained by safer methods.

7. Prospects of rTMS in the study of epilepsy

As a noninvasive, easily applied and safe technology, rTMS may be an effective adjunctive treatment for patients with refractory epilepsy, and may provide a valuable insight into pathophysiological mechanisms underlying epileptic processes and AED-induced changes of the excitability of cortical networks. In addition, rTMS changes induced by different AEDs could be used as a neurophysiological index to optimize the treatment in a given patient. However, the best regimen of rTMS delivering has not been determined. Multiple central collaborative studies are necessary to establish optimum stimulation parameters, such as stimulus frequency, intensity, number of stimuli, train duration, intertrain interval, coil type, and stimulation sites. With study going on, it is probable that rTMS will be an effective therapeutic tool and be widely used in clinical practice. What's more, it is hopeful that the research into mechanisms of epileptogenicity may also break through by using rTMS.

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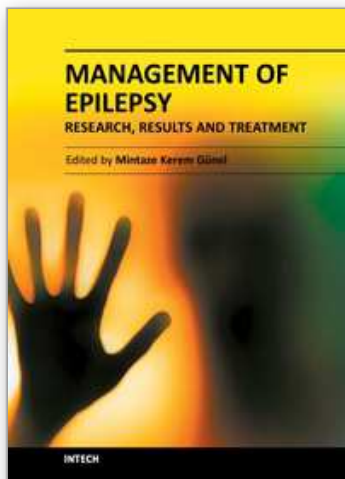
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Management of Epilepsy - Research, Results and Treatment

Edited by Prof. Mintaze Kerem Günel

ISBN 978-953-307-680-5

Hard cover, 194 pages

Publisher InTech

Published online 15, September, 2011

Published in print edition September, 2011

Epilepsy is one of the most common neurological disorders, with a prevalence of 4-10/1000. The book contains the practical methods to approaching the classification and diagnosis of epilepsy, and provides information on management. Epilepsy is a comprehensive book which guides the reader through all aspects of epilepsy, both practical and academic, covering all aspects of diagnosis and management of children with epilepsy in a clear, concise, and practical fashion. The book is organized so that it can either be read cover to cover for a comprehensive tutorial or be kept desk side as a reference to the epilepsy. Each chapter introduces a number of related epilepsy and its diagnosis, treatment and co-morbidities supported by examples. Included chapters bring together valuable materials in the form of extended clinical knowledge from practice to clinic features.

How to reference

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Wang Xiao-Ming and Yu Ju-Ming (2011). The Clinical Application of Transcranial Magnetic Stimulation in the Study of Epilepsy, Management of Epilepsy - Research, Results and Treatment, Prof. Mintaze Kerem Günel (Ed.), ISBN: 978-953-307-680-5, InTech, Available from: <http://www.intechopen.com/books/management-of-epilepsy-research-results-and-treatment/the-clinical-application-of-transcranial-magnetic-stimulation-in-the-study-of-epilepsy>

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