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A facilitation tool: transcranial magnetic stimulation in epilepsy research

Jing Zhou

Stanford University Neurodiagnostic LAB Stanford, CA, USA

Review

Abstract: Transcranial magnetic stimulation (TMS) is a noninvasive and relatively safe method to modulate the cortical activities and thus becomes popular in clinical research such as epilepsy studies. These studies mainly focus on the use of paired-pulse TMS as biomarkers and the effects of repetitive TMS (rTMS) in epilepsy treatment. Paired-pulse TMS measures the cortical excitability under different pathological circumstances by deriving and analyzing paired-pulse recovery curve, which has been proved reliable and widely used to study the physiological and pharmacological mechanisms in epilepsy. rTMS is able to modulate the brain functions and has been considered as a potential treatment for epilepsy, yet the evidence is insufficient and further exploration is required. This review intends to examine the methodologies and outcomes presented by relevant studies and to discuss the pros and cons of current TMS research. This review gives a brief intro-duction to background and principle of TMS. It reviews the methods measuring cortical excitability and the key findings in accordance with the mechanisms of epilepsy. It also reviews the existing controlled studies in therapeutic effectiveness of rTMS and analyzes the advantages of different designs and parameter choices. In the end, this review suggests directions for future research.

Key words: Transcranial magnetic stimulation; TMS; epilepsy; cortical excitability; controlled study; treatment.

Introduction

Transcranial magnetic stimulation (TMS) was first proposed in the middle of the 1980s to stimulate the mo-tor cortex and deep peripheral nerves in humans (1,2). It was then endorsed widely by the clinical neurophysiolo-gists due to its noninvasive approach (3). Since then, TMS have been carried out in different clinical studies: pain, movement or mental disorders, stroke, sclerosis, tinnitus and epilepsy et al (4). The investigation of the antiepi-leptic effects of TMS started in the late 1990s and was followed by a series of single case reports and small scale studies indicating the possibility of TMS application in epilepsy treatment (3). Later controlled studies found that there was a trend towards a short-term decrease in seizure frequency following TMS and that this decrease was grea-ter in patients with neocortical epileptogenic foci, which inspired the notion of TMS therapy (5). Current studies in TMS application in epilepsy can be roughly categorized into two groups. The first group uses TMS as a biomar-ker to explore the influence of the etiology of epilepsy/seizure, epileptogenic foci, drugs, and other physiological parameters on cortical excitability. Studies in this catego-ry have successfully revealed the mechanisms of several factors such as drugs or physiological conditions influen-cing cortical activities at cell level. The other group of studies evaluates the therapeutic effects of repetitive TMS (rTMS), which is known as a train of TMS pulses given to the brain with fixed intensity and frequency, aiming to disrupt or modulate the cortical function on different types of epilepsy (8). The outcomes of this group, however, are susceptible to not only the patients but also the methodo-logies (9). Those studies supporting the therapeutic effects of rTMS ascribed their positive results to proper selec-tion of subjects with superficial epileptogenic foci, precise and focal targeting the foci, and appropriate stimu-lation parameters such as frequency and intensity, which suggest the possibility to reduce the number of epileptic discharges or abnormalities with right choice of patients and methodologies (6,7,10). These studies, showing posi-tive effects or not, are worth further expansion.

In this paper, the influential studies in both categories are reviewed with emphasis on the relation between their parameters and outcomes when implementing TMS. In-sufficiencies of the research are discussed and future ex-pansions are addressed.

Background

Principle of the stimulation

The principle of TMS is Faraday's law of induction. A coil is placed on the scalp and produces a magne-tic field when a powerful and rapidly changing current passes through it. The magnetic field passes through the tissues of the head and induces a weaker electrical current in brain, as shown in Figure 1. The strength of this wea-ker electrical current, which is in proportion to the rate of change of the magnetic field, can be enough to excite neurons in the brain (11). Due to this principle, TMS is noninvasive and relatively painless comparing to other commonly used stimulation methods.

In clinical practice, the path and strength of the in-duced electrical field in brain depends on the following factors: forms and patterns of stimulation, shape and orientation of the coil, and level of excitability of indi-vidual neural elements (12). TMS is usually given in two forms: (1) single-pulse, and (2) paired-pulse, which is a pair of two successive pulses delivered within a short in-

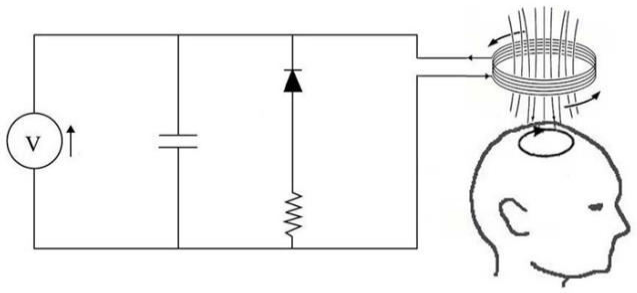

Figure 1. Basic principle of transcranial magnetic stimulation.

terval, varying from a few to hundreds milliseconds (12). In epilepsy research, single-pulse TMS has been adopted in treatment in the form of rTMS, while paired-pulse TMS has been proposed for investigation of cortical excitabi-lity under different circumstances. The waveform of the magnetic pulse affects the efficiency of the stimulation. It has two typical forms: the monophasic and the biphasic. Monophasic pulse is used in single-pulse TMS, whereas biphasic waveform is required in rTMS since its effec-tiveness with regard to excitation threshold and response amplitude meets lower energy requirement (13). Stimula-tion frequency is a decisive pattern to successful cortical modulation by rTMS. rTMS can suppress cortical excita-bility when given at frequencies equal to or lower than 1 Hz. However, it tends to increase cortical excitability tem-porarily when given at frequencies over 20 Hz (14). Be-sides the stimuli, the coil is also found contributing to the effectiveness of TMS. According to several reports, the precise and focal targeting of the coil to the epileptoge-nic foci during stimulation is the prerequisite to achieve positive therapeutic results (7,10). The geometry and pla-cement of the coil determine the activated zone of TMS in brain. To achieve different purposes, coils with various penetration and focalization abilities have been proposed. So far, there are circular coils (round coils), figure-8 coils, Hesed (H) coils, double cone coils, cloverleaf coils, slinky coils, 3D differential coils, and ferromagnetic coils (15). Among these designs, the figure-8 design exhibits the best depth-focalization tradeoff (15). It has been adopted fre-quently in recent studies in epilepsy treatment. Figures 2 and 3 illustrate the appearances and the distributions of magnitude of the electric field underneath a figure-8 coil and another commonly used design, a circular coil (16). As can be seen, the figure-8 design is more focal than the circular one.

The neural basis of inhibition in cortical activities The altered balance between excitation and inhibition in neural membranes is the core factor to transit to the ictal state in the epileptogenic region (17). Synaptic inhibition in the brain is mediated by GABA receptors, which are divided into three classes: GABAA, GABAB, and GABAC. GABAA receptors, which exhibit multiple conductance levels, are the most widespread ionotropic receptors acti-vated by GABA. They lead inhibitory postsynaptic poten-tial and can be blocked or modulated by bicuculline, picro-toxin or anxiolytic benzodiazepines, some of which could induce epileptic discharges (18). GABAB receptors can be coupled to different mechanisms in different neurons and then mediate the inhibitory potential. They present both pre- and post-synaptically. GABAC receptors are predo-minantly in the vertebrate retina (19). Epileptic activity is most strongly affected by GABAA receptors mediated inhibition compared with the other two classes (20).

The activation of GABA receptors can be measured using paired-pulse TMS. The first pulse in the pair, also known as conditioning pulse, elicits a GABA-mediated inhibitory post-synaptic potential to reduce the motor evoked potential (MEP) generated by the second pulse, or test pulse. The activation of GABA receptors is evaluated by measuring the ratio of the amplitudes of two evoked potentials provoked by the paired pulses. When the inter-val between the paired pulses is only a few milliseconds, the ratio reflects the activation of GABAA receptors. When this interval is up to hundreds of milliseconds, the ratio reflects the activation of $GABA_B$ receptors (21).

Methodology and Results

Evaluation of the stimulation

Three variables contribute to the measurement of cor-tical excitability by TMS: (1) the threshold to stimulation, which is measured in the primary motor cortex (M1), known as motor threshold (MT); (2) the duration of the cor-tical silent period (SP); and (3) the corticocortical inhibi-tion and facilitation curve, or paired-pulse recovery curve. The first two variables are mostly measured in single-pulse stimulation, while the third needs to be derived from a se-ries of measurements fulfilled by paired-pulse TMS (17). Conventionally, MT is defined as the lowest stimulation intensity that elicits MEPs with peak-to-peak amplitude over 50 μV in the target muscle in at least 50% of suc-cessive trials (22). It reflects neural membrane excitability and often changes in diseases. SP refers to the electromyo-

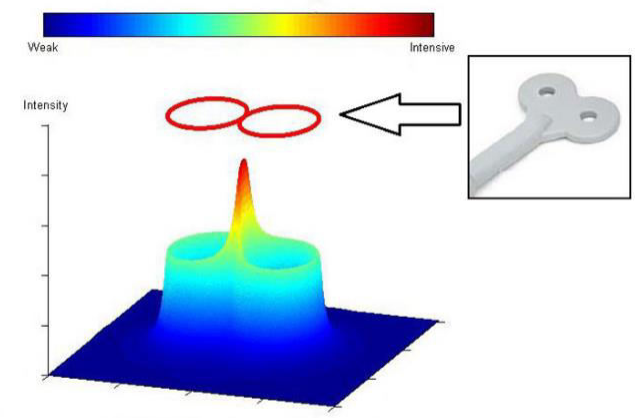

Figure 2. Intensity of TMS evoked electric field by a figure-8 coil and its distribution underneath the figure-8 coil.

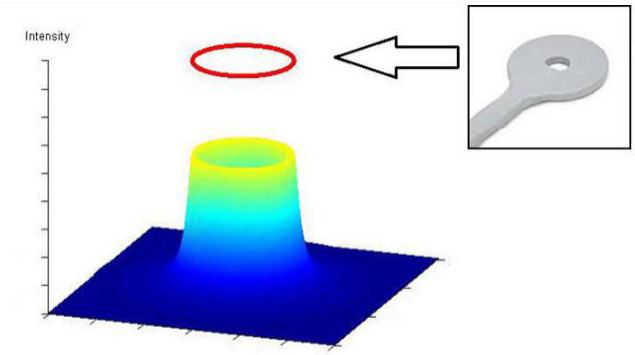

Figure 3. Intensity of TMS evoked electric field by a circular coil and its distribution underneath the circular coil.

graphic suppression period from the end of the evoked po-tential to the return of voluntary electromyographic acti-vity due to inhibitory mechanisms in the motor cortex. SP lasts up to 300ms and is most likely mediated by GABAB receptors (14,23,42). Paired-pulse recovery curve illus-trates the variation of the ratio of the amplitudes of evoked potentials by paired-pulse TMS. As mentioned in Section 2.2, the measurements on the paired-pulse recovery curve with short inter-stimulus intervals as a few milliseconds reflect the level of cortical inhibition mediated by GABAA receptor, while those with long intervals as hundreds of milliseconds are related to the activation of GABAB. Mea-surements with median intervals often show the status of facilitation. However, if the paired-pulse recovery curve shows a trend of facilitation within inhibition ranges, it suggests a loss of GABA-mediated modulation (24,25).

Cortical excitability measurement

As explained in previous sections, cortex functions by the excitatory and inhibitory system in neurons, which is mediated by GABA receptors. Abnormal reorganization of brain circuits disturbs the balance between excitatory and inhibitory activities and leads to neurological disor-ders such as epilepsy. In cortical level, it appears as a trend of seizure onset when the cortical excitability increases (24). Conversely, studies have reported reductions in cor-tical hyperexcitability during antiepileptic treatment (26). Besides the pathological influence, cortical excitability is also affected by physiological and environmental factors. Diurnal variation, hormonal level, sleep, all above have impacts on the cortical excitability (26,28). Badawy et al validated the stability of measurements of cortical exci-tability by TMS across time and demonstrated increased motor cortical excitability as a feature for epilepsy, sug-gesting this measurement can be a reliable biomarker for diagnosis (27).

Cortical excitability is scaled using paired-pulse reco-very curve. To study the short-interval intracortical inhi-bition (SICI) mediated by GABAA, paired-pulse TMS are delivered with subthreshold condition stimuli and supra-threshold test stimuli. The intensity of the condition sti-mulus is usually set at 70-90% of the MT, while that of the test stimulus is at 110-130% of the MT (43,44). The volleys originating from both direct stimulations and sy-naptic activation of corticospinal neurons are suppressed at an inter-stimulus interval of 1 millisecond and are se-lectively inhibited when the interval is 3-5 milliseconds. There is an intracortical facilitation (ICF) period of 10-15 milliseconds after the condition stimulus (42). The ratio of the peak-to-peak amplitude of the response to the test stimulus to that of a baseline response, which is evoked by stimulus delivered at the intensity of the test stimuli in paired-pulse TMS without any preconditioning stimu-li, is calculated as the biomarker (27). In the studies of long-interval intracortical inhibition (LICI), two succes-sive suprathreshold stimuli, usually at the same intensity with the baseline stimuli, are delivered with inter-stimulus intervals of 50-300 ms (42,45). In this period, the volleys originating from synaptic activation are affected, which coincides with the timing of GABAB receptor activation (42). The ratio of the peak-to-peak amplitude of the res-ponse to the second stimulus in the paired-pulse TMS to that of the first stimulus is used as in SICI studies (27). To fully depict the trend of inhibition and facilitation in cor-tex through the timeline, several intervals that represent the key time points are implemented respectively. Those used most frequently are 2, 5, 10, 15 milliseconds for SICI and 100, 150, 200, 250, 300 milliseconds for LICI (28,30,31,32). To reduce the noise in EEG signal and to derive generalized results, an average of the responses to around ten stimuli is adopted to represent each condition, including baseline. To keep the equality of different condi-tions, the inter-stimulus interval is randomly selected until the expected number for each pair of stimuli is reached. Interval between adjacent pairs is 5-15s in order to main-tain mutual independence of the stimuli (27,43).

Studies on exploring the factors that influence the cor-tical excitability have been done based on these measure-ments for years. A series of publications on this topic has been contributed and the highlights of the findings are gui-dance of future therapeutic directions. For example, stu-dies showed that cortical excitability increased in 24 hours before a seizure and then reduced remarkably in 24 hours after a seizure (24). Increase in cortical excitability was observed in the hemisphere ipsilateral to the seizure focus whereas the contralateral hemisphere remained normal in drug naive patients with new onset temporal lobe epilepsy (28). For the patients with refractory seizures, cortical ex-citability increased in both hemispheres even when the subjects were taking significant number of antiepileptic drugs. From the therapeutic viewpoint, these patients had already developed drug resistances. Compared to the two seizure-onset types, seizure-free patients demonstrated almost normal cortical excitability. This finding revealed the characteristics of cortical hyperexcitability in diffe-rent types of patients and indicated that this abnormality was reversible under certain conditions (28). The motor cortical excitability was influenced in varying degrees by most focal epilepsy syndromes, regardless the epileptoge-nic foci (29,46). Cortical excitability of patients with ju-venile myoclonic epilepsy was higher than that of either the juvenile absence epilepsy or generalized epilepsy with tonic-clonic seizures, while all three types of epilepsy caused significant cortical hyperexcitability (30,45). De-pending on different types of generalized epilepsy, both GABAA and GABAB mediated inhibition reduced in some degree. Although different types of epilepsy were under-lain by different mechanisms, there was still an inclination that some physiological and environmental factors can precipitate seizures (31). For example, sleep deprivation can effectively provoke generalized and focal interictal discharges in patients with idiopathic generalized epi-lepsy (32). Seizures were also found common in patients suffering from severe hypoglycemia (31). Even circadian change and menstrual cycle exhibited correlations with seizure occurrence (33,47). These inclinations have been found in accordance with the levels of cortical excitability under corresponding circumstances by developing their paired-pulse recovery curves (31,32,33,47).

With TMS as a high-credibility biomarker for cortical excitability measurement, pharmacologic effects can be investigated (34). TMS has revealed some mechanisms of synaptic plasticity such as GABAergic neurotransmission under the pharmacologic influence and the way to modu-late them pharmacologically (34,39,48). Measuring corti-cal excitability by TMS has assisted comparison between drug effects and understanding of pharmaco-physiologic properties (43,49,50).

Therapeutic exploration

As a noninvasive method to modulate neuronal activi-ties, the therapeutic effect of TMS, particularly rTMS, has been explored frequently. Most of the explorations were case reports and open-label or randomized trials, which showed high dependence on individual parameters and variance in methodologies (8). Controlled study can limit the uncertain parameters and reveal the effective factors. However, only a limited number of controlled studies have been performed due to practical reason, and they failed to yield consistent results to support the notion of antiepilep-tic effects of TMS (35). Despite their disparate outcomes, it is still worth examining these controlled studies to sum up the patterns that favored this therapy. In total, there are six controlled studies with full description in methodolo-gies and results. Table 1 shows their primary parameters.

Theodore et al performed one of the earliest controlled TMS studies, when optimal choices of parameters were still vague. This study recruited 24 patients, who suffe-red from at least one drug-resistant complex partial or se-condarily generalized seizure with foci mainly in mesial temporal and lateral temporal neocortex. Patients were divided into active group receiving genuine treatment and controlled group receiving placebo. The daily treat-ment was given in two 15-minute sessions by a figure-8 coil with stimulation frequency at 1 Hz and intensity at 120% of MT. For patients in controlled group, the coil was angled at 90 degrees away from the scalp to neutralize the stimulation. The treatment was continued for one week. Two evaluations were done respectively at the second and eighth week after stimulation. During the entire proce-dure, the patients were on their constant antiepileptic drug regimens (5). An improvement of 16% mean reduction in weekly seizure frequency was discovered in the active group two weeks after stimulation, while there was only 1% reduction observed in the controlled group. However, the mean seizure frequency reduction of the active group slipped back to 4.5% after eight weeks and that of the controlled group slipped to 0.4%, which indicated the im-provement in the first two post-stimulation week was tran-sient (5). This research also discovered that the treatment had a preference on patients with lateral temporal neocor-tical foci in the active group. The mean seizure frequency reduction of these patients was 24% at the second week and 7% at the eighth week, while the corresponding re-ductions of patients with mesial temporal foci were -11% and 3% (5). Theodore et al attributed the short-term effect of treatment to a slightly high stimulation frequency and inadequate treatment period. They also pointed out the di-sadvantage to stimulate the mesial temporal foci, consi-dering the rapid attenuation of magnetic field in scalp (5). This study, though not prominent, provided information

Table 1. Controlled studies in therapeutic effects of rTMS.

	Patient#	Stimulation protocol	Strategy for controlled group	Reduction of seizure frequency
Seynaeve 2015	11	main epilepsy type: focal, coil: figure-8, round, frequency: 0.5Hz, intensity: 90% of MT, prescription: three 500-stimuli sessions daily for 2 consecutive weeks for both active tests	use sham coil	no
Sun 2012	60	main epilepsy type: frontal or central-parietal, coil: figure-8, frequency: 0.5Hz, intensity: 90% of MT, prescription: three 500-stimuli sessions daily for 2 consecutive weeks	stimulate at 20% of MT	yes
Cantello 2007	43	main epilepsy type: neocortical, coil: round, frequency: 0.3Hz, intensity: 100% of MT, prescription: two 500-stimuli sessions daily for 5 consecutive days	overlap two coils and trigger the one away no from scalp	
Fregni 2006	21	main epilepsy type: focal, coil: figure-8, frequency: 1Hz, intensity: 70% of maximum stimulator output, prescription: 20-minute session daily for 5 consecutive days	use sham coil	yes
Tergau 2003	17	main epilepsy type: focal neocortical, coil: round, frequency: 0.333 and 1Hz, intensity: slightly below MT, prescription: 500 clockwise-current pulses plus 500 anti-clockwise-current pulses daily for 5 consecutive days for both active tests	use sham coil with 0.666Hz stimulation yes frequency	
Theodore 2002	24	main epilepsy type: mesial temporal, lateral temporal neocortical, coil: figure-8, frequency: 1Hz, intensity: 120% of MT, prescription: two 15-minute sessions daily for 1 week	angle the coil at 90 degrees away from mild the scalp	

and a benchmark for later studies.

Tergau et al gave an interim report of their multicenter cross-over placebo-controlled study one year after Theo-dore's report (7). This study included 17 patients, 11 of whom were diagnosed as focal neocortical epilepsy. Each patient went through three treatment periods, which were arranged in random order. Two of the treatment periods were active stimulations with different frequencies at 1Hz and 0.333Hz by a round coil. The stimulation intensity was set slightly below MT. Another treatment period was placebo with stimulation frequency at 0.666Hz. In the placebo stimulation, the coil was specially designed to produce 10% magnetic field intensity of the normal coil but with similar noise and skin sensation. Each treatment period lasted 5 consecutive days, while 500 monopolar stimuli with clockwise current direction followed by 500 stimuli in anti-clockwise direction were given daily. Indi-vidual treatment periods were separated by at least eight weeks to satisfy a minimum four-week observation phase before and after each treatment. Medication regimen was constant during the study (7). In the rTMS treatment at 0.333Hz, the seizure frequency was reduced to less than 60% compared to baseline and the seizure reduction on average was 30%-40% over two post-stimulation weeks, while no discernible effect was observed in either placebo or rTMS treatment at 1Hz. Tergau et al emphasized the importance of stimulation frequency in cortical activity modulation, which could be the key factor to the positive outcome of this study (7).

Fregni et al led another randomized, double-blind, controlled study with emphasis on patients having malfor-mations of cortical development, who may be more res-ponsive to rTMS (36). This study recruited 21 patients, 17 among whom had single focal epileptogenic foci while the rest 4 patients had diffuse abnormalities. These patients were randomly divided into active group consisting of 12 subjects and sham group consisting of 9 subjects. Both groups used the same protocol except the coil. The active group was adopting a normal figure-8 coil, while the sham group was using a special coil with only similar appea-rance and sound artifact. The coil was targeting the epilep-togenic foci during stimulation. For patients with diffuse abnormalities, Cz was chosen as the target. Unlike other studies using MT to determine the stimulation intensity, Fregni et al chose a fixed intensity at 70% of the maxi-mum output of the stimulator. A daily 20-minute stimula-tion session at 1Hz was given for five consecutive days. During the entire study, patients continued their usual an-tiepileptic drug dose unless for clinical reason (36). The outcomes were evaluated respectively at second, fourth, eighth week after treatment. According to the post-simu-lation observation, active group achieved a significant re-duction of 72% in seizure frequency two weeks after the treatment when compared to the baseline. Three patients were seizure free and ten patients had a reduction over 50% in seizure frequency during these two weeks. On the other hand, the sham group showed no significant change. This beneficial effect in active group continued till the eighth post-simulation week, the last week of observation, when the reduction in seizure frequency remained signi-ficant at 58% of the baseline. A 31% reduction in the nu-mber of epileptic discharges was also observed in active group immediately after the five-day treatment. However, this effect faded out in following weeks (36). Fregni et al highlighted two aspects that led to the positive outcome: (1) proper selection of subjects, (2) suitable sham design. In this study, all patients had epileptogenic foci locating on cortical convexity, which can be easily targeted and reached by TMS. The placebo also appeared to reliably blind participants (36).

Despite the positive outcomes demonstrated by two previous studies, Cantello et al reported a controlled stu-dy on a 43-subject group, showing negative clinical ef-fect (6). This study involved 43 drug-resistant patients, 34 of whom had partial neocortical epilepsy. Each pa-tient received two treatments, active and sham. The two treatments were separated by six weeks and their order was randomly assigned for individual. The treatment was a 5-day procedure, consisting of two 500-stimuli rTMS sessions with intensity of 100% MT at 0.3 Hz daily. Two overlapped circular coils were adopted. In the active treat-ment, only the coil directly contacting the scalp was trig-gered, while the other coil was triggered alone in the sham treatment. Thus the patient was supposed to have identical perception (6). Each treatment was assessed in following six weeks and the results were compared to baseline. The study observed a slight average decrease of 9-15% of the seizure frequency in the first two post-stimulation weeks in both treatments, which was not enough to declare rTMS efficient. This insignificant decrease faded out at the fourth post-stimulation week. However, a significant proportion of patients showed decrease in the number of epileptic abnormalities after active but not sham treatment (6). Cantello et al ascribed the negative results to large inter-individual variability among the test group, mainly caused by heterogeneous underlying pathology and heavy drug regimens (6).

Recently, Sun et al reported a randomized single-blinded controlled study with prominent outcome (10). This study included 60 patients with single epileptogenic foci, 47 in frontal or central-parietal cortex. Each patient received daily treatment consisting of three sessions of 500 stimuli at 0.5 Hz for two weeks. In this procedure, patients were randomly assigned to active or controlled group. The active group received high intensity rTMS at 90% of MT while the controlled group received low in-tensity rTMS at 20% of MT. The epileptogenic focus was determined by the patient's EEG clinical semiology and MRI scan results and targeted by a figure-8 coil (10). After the treatment, patients were followed up by eight weeks and their seizure diaries were assessed. Individual daily dose of antiepileptic drugs was unchanged throughout the study. Compared to baseline, the active group showed an average decrease of 79.8% in seizure frequency, while this decrease is 2.3% in controlled group. The active group also had an 80.6% greater reduction in seizure frequen-cy than the controlled group in the first post-stimulation week. Besides, the median time that the first post-stimula-tion seizure occurred was over six weeks for active group but one week for controlled group (10). As Fregni's study did, Sun et al emphasized the importance of proper selec-tion of subjects and precise targeting of the epileptogenic foci to positive outcome (10,36). In Sun's study, the majo-rity of patients had frontal and central-parietal foci, which were superficial for the magnetic field to reach efficiently.

For comparison, two patients in active group with medial temporal foci showed poor efficacy (10). This study also provided information in changes of daily seizure frequen-

cy. It is noteworthy that although the seizure frequency in active group kept decreasing since the beginning of the treatment, it bounced back temporarily around the fifth day of the treatment. This fluctuation was not discussed in the report but it is worth further exploration (10).

Sun's study appeared to be the largest controlled stu-dy so far and it highly supported the notion of therapeu-tic effect of rTMS. However, Seynaeve et al conducted a randomized controlled cross-over study with a similar protocol later, showing negative results (37). Eleven pa-tients participated in this study, all having refractory fo-cal epilepsy and single epileptogenic zone. Each of them was supposed to receive three treatments with application of figure-8 coil, round coil, and sham coil respectively. The order of the three treatments was randomized indivi-dually. The treatment was a two-week procedure, inclu-ding 10 daily sessions. In each session, 1500 stimuli were given at 0.5Hz with an intensity of 90% MT. The coils were oriented to be perpendicular to the nearest important sulcus, which was determined by 3D MRI reconstruction. Each treatment was followed by a ten-week observation period and the outcomes were compared with baseline and each other. Due to clinical reason, four patients failed to complete all treatments and partial results were used for analysis in these cases (37). Observation showed no signi-ficant difference in mean seizure frequency in any treat-ments compared to baseline or each other. Nevertheless, improvement in seizure frequency was still observed in two individuals. One patient had seizure reduction up to 48% after all three treatments. The other patient had over 50% seizure reduction in both active treatments in the first post-stimulation month, yet it was back to baseline level in the following weeks. Besides, over one third patients experienced side effects, including hearing problems, headache and fatigue. Two patients even had increases in seizure frequency (37). This study carefully excluded patients with mesial temporal lobe epilepsy and multifo-cal epilepsy in order to facilitate the stimulation. It also adopted strategies used in previous positive studies, yet still yielding a negative result. Seynaeve et al attributed the negative result to insufficient stimulation intensity and neurophysiologic differences between subjects (37).

Although only a few controlled studies in therapeu-tic rTMS have been done, they revealed certain patterns. Three out of six controlled studies yielded positive results to justify the effectiveness of TMS therapy (7,10,36). Compared to the other negative studies, they adopted strategies that allowed the magnetic field to work more efficiently. First, they mainly selected subjects with fo-cal epilepsy and superficial foci so the TMS can act on epileptogenic zones thoroughly (7,10,36). Notice that the mild-result case included over 40% subjects with mesial temporal foci, which is difficult for TMS to reach (5). In one negative case, Seynaeve et al. carefully selected pa-tients with focal neocortical foci. However, the coil was set to target the nearest sulcus, which might affect the ac-curacy of coil orientation and the actual depth of the sti-mulation spot (37). Figure-8 coil, which theoretically has the best depth-focalization tradeoff, was adopted alone in three studies, yielding one mild and two positive results (5,10,15,36). Round coil was used alone in two studies, yielding one positive and one negative result (6,7). Both coils were used in Seynaeve's study, yielding a negative result (37). Although the evidence was not sufficient, figure-8 coil showed better efficacy in stimulating focal, superficial epileptogenic zones in controlled studies. Re-levant research sustained focal stimulation by showing its better therapeutic effect than that of non-focal stimulation (40). The choice of stimulation frequency was also dis-cussed. TMS in high frequency, mainly 5-100Hz, were reported to be ineffective in reducing spike frequency (53). All six controlled studies chose frequencies no more than 1Hz. Theodore and Tergau et al. suggested that even 1Hz was not sufficient to induce inhibition for some pa-tients (5,7). Tergau et al. demonstrated a strong case that 0.333Hz was superior to 1Hz (7). Several studies showed the effectiveness of 0.5Hz rTMS (10,40,41). The mecha-nisms of stimulation frequency are still unknown but there is a high possibility that the susceptibility to inhibitory and excitatory rTMS varies in a large extent by individual
(7). Stimulation intensity, though not being emphasized, showed its influence in Sun's case (10). Stimulation length may also affect the outcome considering the bounce-back seizure frequency around the fifth day of the treatment in Sun's study (10). Besides the stimulation strategies, it is noteworthy that all studies chose to continue patients' re-gimes rather than to stop them. The doses of anti-epileptic drugs for patients were not listed yet two studies attributed their negative results to the heavy doses (6,37). There is no controlled study in drug effects in rTMS therapy so far. Further exploration is necessary.

The notion that low-frequency rTMS lead to inhibition in cortex is consistent with the evidences found in several controlled studies. Besides the controlled studies, many open label studies have made attempts in treating epilepsy with rTMS. Most of these studies were conducted during the interictal state as the controlled studies were, yet rTMS can also be applied during the ictal state and prelimina-ry studies showed its efficacy in suppress seizures (38). Although there are still many questions remained and the underlying mechanisms are not fully uncovered, rTMS is still considered as a novel, prospective and relatively safe therapeutic method.

Discussion

TMS has been proved as an efficient and stable tool in pathological mechanism investigation. Cortical exci-tability measured by paired-pulse TMS is a prospective biomarker, since it manifests the key to the development of epilepsy, imbalance of inhibition and excitation (42). However, high inter-subject variability has still been re-ported. Three factors are considered to contribute to the inconsistencies: (1) recruitment of drug-treated patients,
(2) methodological differences between studies, and (3) poor correlation of the TMS to the clinical variables (9). Drug effects are believed to distort the outcomes most severely, yet most studies still performed experiments on subjects taking anticonvulsants (9). One solution is to ob-tain full intensity curves with the same intensities of the conditioning stimulus before and after drug application, which will allow comparison between changes (51). Mul-tiple testing also helps eliminate the variations (51). On the other hand, this justifies the examination of drug ef-fects through cortical excitability with TMS. The limita-tion of TMS based pharmacodynamics studies lies in the transferability of results from healthy subjects to patients, due to their different responses to TMS or drugs (50).

Despite the limitation, pharmaco-TMS is still a promising field in human cortical physiology.

rTMS has been reported to reduce cortical excitability and thus to suppress epilepsy (35). Existing controlled stu-dies have suggested effective strategies in applying thera-peutic rTMS, including stimulation frequency, intensity, length of treatment, choice of patients, and orientation of coil, et al. The studies have been able to precisely target epileptogenic zone using the patient's MRI scan and EEG clinical semiology, and to effectively stimulate the super-ficial foci (10). Yet disagreements still exist among these studies even using similar protocols, requiring further discussion. First, there is no explanation for the negative results in population with focal neocortical foci. Context indicated it may be caused by previous surgeries or the orientation strategies (37). Statistical test might help the analysis of interclass variations. Second, the optimal sti-mulation frequency, intensity and length remain unknown. Stimulation frequency is considered crucial in rTMS yet the effect varies in population (7). The therapeutic effects of rTMS may be improved if future research can develop a standard procedure to determine optimal stimulation pa-rameters for individual. Third, the effects of concomitant anti-epileptic drugs have been underestimated and need further study.

Despite the progress in exploring the therapeutic ef-fects of TMS, there are still criticisms on existing metho-dologies, especially on the designs of placebo stimulation (52). The two prevalent placebo designs, tilted coil and sham coil, have been considered defective. The approach that uses tilted coil as placebo causes difficulties to deter-mine whether or not there is residual brain stimulation, while the use of sham coil abolishes the somato-sensory effects and peripheral nerve stimulation evoked by active TMS. For the patients who have already received consi-derable information about TMS, the blinding may not be successful. Between-subject designs have worked rela-tively better than within-subject

designs, yet the latter are much more common (52). The investigation of placebo effects has also been insufficient and ignored in TMS re-search (52). Current designs of placebo in TMS research are limited and should be balanced with other methodolo-gies in future.

Besides the defects in the design of controlled studies, concerns about safety issue and side effects also remain in TMS studies. The magnetic field generated by TMS can excessively heat some highly conductive electrodes and thus cause skin burns. Some brain implants would not only be heated up, resulting in irreversible brain tissue damage, but also be displaced due to the induced force. For delicate implants such as cochlear implants, the TMS pulse could damage their antennae and electronic chips (53). Significant side effects linked with TMS include hearing impairment, headache, pain, transient hypomania, and seizures, which is the worst among all. Seizures were reported to be induced in previous studies, though less than 2%, when rTMS were implemented in relatively high frequencies (11,53). The lowest known frequency that in-duced seizures is 3Hz, with stimulation intensity at 130% of MT (11). There was no report on rTMS induced sei-zures when the frequency was less than or equal to 1Hz in the past (53). These risks, though minor, should not be ne-glected in future studies. To prevent the above risks, TMS procedures should strictly follow a pre-specified protocol

with thorough consideration.

Significant efforts have been contributed in the field of TMS application in epilepsy in the last two decades. As a noninvasive strategy, TMS provides an innovative and relatively safe way to study the brain mechanisms. It has demonstrated its effectiveness as a biomarker for cortical excitability and potential use in epilepsy treatment. Future research should reexamine the inconsistency of previous studies and cover the methodological insufficiencies. Other strategies such as EEG, MRI need to be integrated into research for better analysis. TMS as a biomarker will be furthered to intrinsic measures such as functional connectivity (54).

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