Epilepsy

Rev Med Suisse. 2005 Sep 21;1(33):2162-4, 2166.

[Novel brain stimulation techniques: therapeutic perspectives in psychiatry]

[Article in French]

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Recent advances have allowed the development of new physical techniques in neurology and psychiatry, such as Transcranial Magnetic Stimulation (TMS), Vagus Nerve Stimulation (VNS), and Deep Brain Stimulation (DBS). These techniques are already recognized as therapeutic approaches in several late stage refractory neurological disorders (Parkinson's disease, tremor, epilepsy), and currently investigated in psychiatric conditions, refractory to medical treatment (obsessive-compulsive disorder, resistant major depression). In Paralell, these new techniques offer a new window to understand the neurobiology of human behavior.

Curr Psychiatry Rep. 2005 Oct;7(5):381-90.

Transcranial magnetic stimulation for the treatment of depression in neurologic disorders.

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Depression is commonly associated with neurologic disorders. Although depression in neurologic conditions often is associated with a negative impact on quality of life, it frequently is poorly managed. Some factors, such as a multidrug regimen, lack of efficacy, and side effects of antidepressants may explain why depression is not adequately treated in patients with neurologic disorders. Therefore, this population needs new approaches for depression treatment, and repetitive transcranial magnetic stimulation (rTMS) may be one of them because it has been shown to be effective for the treatment of depression alone and depression in certain neurologic diseases such as Parkinson's disease and stroke. rTMS is a noninvasive, focal, and painless treatment associated with

few, mild side effects. It may be effective in the treatment of neurologic diseases such as Parkinson's disease, stroke, and epilepsy. In this paper, we discuss the potential risks and benefits of rTMS treatment for depression in Parkinson's disease, epilepsy, stroke, multiple sclerosis, and Alzheimer's disease. Lastly, a framework that includes the parameters of stimulation (intensity, frequency, number of pulses, and site of stimulation) for the treatment of depression in neurologic diseases is proposed.

Seizure. 2005 Sep;14(6):387-92.

Low-frequency repetitive transcranial magnetic stimulation for seizure suppression in patients with extratemporal lobe epilepsy-a pilot study.

Kinoshita M, **Ikeda A**, **Begum T**, **Yamamoto J**, **Hitomi T**, **Shibasaki H**.

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We evaluated the effect of low-frequency repetitive transcranial magnetic stimulation (rTMS) on seizure frequency in adult patients with medically intractable extratemporal lobe epilepsy (ETLE). Seven patients with medically intractable ETLE received low-frequency rTMS at 0.9 Hz, basically two sets of 15 min stimulation per day for five days in a week, with the stimulus intensity of 90% of resting motor threshold (RMT). The number of seizures during two weeks before and after the stimulation of one week was compared. Furthermore, RMT and active motor threshold (AMT) were measured before and after rTMS for each daily session. After low-frequency rTMS of one week, the frequency of all seizure types, complex partial seizures (CPSs) and simple partial seizures was reduced by 19.1, 35.9 and 7.4%, respectively. The patients with smaller difference between RMT and AMT before rTMS had higher reduction rate of CPSs. A favorable tendency of seizure reduction, though not statistically significant, during two weeks after low-frequency rTMS was demonstrated in medically intractable ETLE patients. As far as CPSs are concerned, smaller decrease of motor threshold by voluntary muscle contraction was associated with better response to rTMS.

Epilepsy Behav. 2005 Sep;7(2):182-9.

Transcranial magnetic stimulation treatment for epilepsy: can it also improve depression and vice versa?

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Comorbidity with depression is an important determinant of the quality of life for patients with epilepsy. Antidepressant medications can effectively treat depression in epileptic

patients, but drug-drug interactions and epileptogenic effects of these drugs pose therapeutic challenges. The mood-stabilizing effects of antiepileptic medications may not be sufficient to treat depression. Therefore, treatments that alleviate the burden of depression without increasing seizure risk or, better yet, with the possibility of improving seizure control are worth exploring. Neuroimaging techniques, such as functional magnetic resonance imaging, are providing novel insights into the pathophysiology of depression in epilepsy. For example, there appears to be prominent brain prefrontal hypoactivity, which may be sustained by the hyperactivity of the seizure focus. If so, neuromodulatory approaches that suppress epileptic focus hyperactivity and concurrently enhance prefrontal activity may be ideally suited. Indeed, vagus nerve stimulation has been shown to yield simultaneous antiseizure and mood effects. Another neuromodulatory technique, transcranial magnetic stimulation (TMS), can also modulate brain activity, but in a noninvasive, painless, and focal manner. Depending on the stimulation parameters, it is possible to enhance or reduce activity in the targeted brain region. Furthermore, TMS has been shown to be effective in treating depression, and preliminary data suggest that this treatment may also be effective for epilepsy treatment. This article reviews these data and explores further the question of whether depression and epilepsy can be simultaneously treated with TMS for optimal therapeutic impact.

Seizure. 2005 Sep;14(6):387-92.

Low-frequency repetitive transcranial magnetic stimulation for seizure suppression in patients with extratemporal lobe epilepsy-a pilot study.

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Department of Neurology, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaharacho, Sakyoku, Kyoto 606-8507, Japan.

We evaluated the effect of low-frequency repetitive transcranial magnetic stimulation (rTMS) on seizure frequency in adult patients with medically intractable extratemporal lobe epilepsy (ETLE). Seven patients with medically intractable ETLE received low-frequency rTMS at 0.9 Hz, basically two sets of 15 min stimulation per day for five days in a week, with the stimulus intensity of 90% of resting motor threshold (RMT). The number of seizures during two weeks before and after the stimulation of one week was compared. Furthermore, RMT and active motor threshold (AMT) were measured before and after rTMS for each daily session. After low-frequency rTMS of one week, the frequency of all seizure types, complex partial seizures (CPSs) and simple partial seizures was reduced by 19.1, 35.9 and 7.4%, respectively. The patients with smaller difference between RMT and AMT before rTMS had higher reduction rate of CPSs. A favorable tendency of seizure reduction, though not statistically significant, during two weeks after low-frequency rTMS was demonstrated in medically intractable ETLE patients. As far as CPSs are concerned, smaller decrease of motor threshold by voluntary muscle contraction was associated with better response to rTMS.

J Neurol Sci. 2005 Jul 15;234(1-2):37-9.

Low-frequency transcranial magnetic stimulation for epilepsia partialis continua due to cortical dysplasia.

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The potential therapeutic role of repetitive transcranial magnetic stimulation (rTMS) in epilepsy has been increasingly recognized. We investigated the effects of low-frequency rTMS in a patient with epilepsia partialis continua (EPC) due to cortical dysplasia. A 31-year-old female patient experienced EPC in the right upper and lower extremities, which had lasted for 15 years without generalized seizures. MRI showed focal megaencephaly around the motor cortex suggestive of cortical dysplasia. A figure of eight magnetic coil was placed over the hand motor area, and 100 stimuli with an intensity at 90% of motor threshold were given at 0.5 Hz. Immediately after rTMS, EPC was nearly abolished. The effects had continued approximately for 2 months, and the second trial resulted in the similar effects and time-course. Low-frequency rTMS was safe and well tolerated in this patient. These findings support the concept that rTMS decreases cortical excitability, and may be an effective treatment for focal partial seizures.

J ECT. 2005 Jun;21(2):88-95.

Transcranial magnetic stimulation in persons younger than the age of 18.

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OBJECTIVES: To review the use of transcranial magnetic stimulation (single-pulse TMS, paired TMS, and repetitive TMS [rTMS]) in persons younger than the age of 18 years. I discuss the technical differences, as well as the diagnostic, therapeutic, and psychiatric uses of TMS/rTMS in this age group. METHODS: I evaluated English-language studies from 1993 to August 2004 on nonconvulsive single-pulse, paired, and rTMS that supported a possible role for the use of TMS in persons younger than 18. Articles reviewed were retrieved from the MEDLINE database and Clinical Scientific index. RESULTS: The 48 studies reviewed involved a total of 1034 children ages 2 weeks to 18 years; 35 of the studies used single-pulse TMS (980 children), 3 studies used paired TMS (20 children), and 7 studies used rTMS (34 children). Three studies used both single and rTMS. However, the number of subjects involved was not reported. CONCLUSIONS: Single-pulse TMS, paired TMS, and rTMS in persons younger than 18 has been used to examine the maturation/activity of the neurons of various central nervous system tracts, plasticity of neurons in epilepsy, other aspects of epilepsy,

multiple sclerosis, myoclonus, transcallosal inhibition, and motor cortex functioning with no reported seizure risk. rTMS has been applied to psychiatric disorders such as ADHD, ADHD with Tourette's, and depression. Adult studies support an antidepressant effect from repetitive TMS, but there is only one study that has been reported on 7 patients that used rTMS to the left dorsal prefrontal cortex on children/adolescents with depression (5 of the 7 subjects treated responded). Although there are limited studies using rTMS (in 34 children), these studies did not report significant adverse effects or seizures. Repetitive TMS safety, ethical, and neurotoxicity concerns also are discussed.

Neurobiol Dis. 2005 Jun-Jul;19(1-2):119-28.

Repetitive low-frequency stimulation reduces epileptiform synchronization in limbic neuronal networks.

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Deep-brain electrical or transcranial magnetic stimulation may represent a therapeutic tool for controlling seizures in patients presenting with epileptic disorders resistant to antiepileptic drugs. In keeping with this clinical evidence, we have reported that repetitive electrical stimuli delivered at approximately 1 Hz in mouse hippocampus-entorhinal cortex (EC) slices depress the EC ability to generate ictal activity induced by the application of 4-aminopyridine (4AP) or Mg(2+)-free medium (Barbarosie, M., Avoli, M., 1997. CA3-driven hippocampal-entorhinal loop controls rather than sustains in vitro limbic seizures. J. Neurosci. 17, 9308-9314.). Here, we confirmed a similar control mechanism in rat brain slices analyzed with field potential recordings during 4AP (50 microM) treatment. In addition, we used intrinsic optical signal (IOS) recordings to quantify the intensity and spatial characteristics of this inhibitory influence. IOSs reflect the changes in light transmittance throughout the entire extent of the slice, and are thus reliable markers of limbic network epileptiform synchronization. First, we found that in the presence of 4AP, the IOS increases, induced by a train of electrical stimuli (10 Hz for 1 s) or by recurrent, single-shock stimulation delivered at 0.05 Hz in the deep EC layers, are reduced in intensity and area size by low-frequency (1 Hz), repetitive stimulation of the subiculum; these effects were observed in all limbic areas contained in the slice. Second, by testing the effects induced by repetitive subicular stimulation at 0.2-10 Hz, we identified maximal efficacy when repetitive stimuli are delivered at 1 Hz. Finally, we discovered that similar, but slightly less pronounced, inhibitory effects occur when repetitive stimuli at 1 Hz are delivered in the EC, suggesting that the reduction of IOSs seen during repetitive stimulation is pathway dependent as well as activity dependent. Thus, the activation of limbic networks at low frequency reduces the intensity and spatial extent of the IOS changes that accompany ictal synchronization in an in vitro slice preparation. This conclusion supports the view that repetitive stimulation may represent a potential therapeutic tool for controlling seizures in patients with pharmaco-resistant epileptic disorders.

Neuron. 2005 Jan 20;45(2):181-3.

Toward establishing a therapeutic window for rTMS by theta burst stimulation.

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In this issue of Neuron, Huang et al. show that a version of the classic theta burst stimulation protocol used to induce LTP/LTD in brain slices can be adapted to a transcranial magnetic stimulation (TMS) protocol to rapidly produce long lasting (up to an hour), reversible effects on motor cortex physiology and behavior. These results may have important implications for the development of clinical applications of rTMS in the treatment of depression, epilepsy, Parkinson's, and other diseases.

Neurology. 2004 Dec 14;63(11):2051-5.

Cortical excitability in drug-naive patients with partial epilepsy: a cross-sectional study.

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OBJECTIVE: To use paired-pulse transcranial magnetic stimulation (TMS) to investigate cortical excitability in drug-naive patients with partial epilepsy. METHODS: Twenty-one drug-naive patients with partial epilepsy and 15 control subjects were studied. The relaxed threshold to TMS, the central silent period, and the intracortical inhibition/facilitation were measured. Statistics implied cluster analysis methods. Also assessed were the patient interictal EEG epileptiform abnormalities (EAs) on a semiquantitative basis. Then the TMS was contrasted to the clinical and EEG findings, using chi2 or Fisher exact tests. RESULTS: One-third of the patients made up a "pathologic" cluster with a disrupted intracortical inhibition ($p < 0.01$). Two-thirds had a normal inhibition. Interictal EAs predominated in the pathologic cluster, for frequency ($p < 0.04$), duration ($p < 0.04$), and focality ($p < 0.02$). CONCLUSIONS: Intracortical inhibition, which was impaired in one-third of the patients, reflects gamma-aminobutyric acid (GABA) activity within cortical area 4. Defective GABA inhibition is a typical pathogenic factor in partial epilepsy. Transcranial magnetic stimulation proved able to detect it. The weaker cortical inhibition had a direct relation to the severity of interictal epileptiform abnormalities.

Child Adolesc Psychiatr Clin N Am. 2005 Jan;14(1):193-210, viii-ix.

Electroconvulsive therapy and repetitive transcranial magnetic stimulation in children and adolescents: a review and report of two cases of epilepsia partialis continua.

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Brain stimulation for the treatment of psychiatric disorders has received increasing attention over the past decade. The introduction of experimental means to stimulate the brain noninvasively with magnetic fields not only has raised interest in these novel means of modulating brain activity but also has refocused attention on a mainstay in the treatment of severe major depression and other disorders (electroconvulsive therapy). This article reviews the current state of knowledge concerning the use electroconvulsive therapy, repetitive transcranial magnetic stimulation, and magnetic seizure therapy in children and adolescents. Two cases of medically intractable epilepsia partialis continua are presented to add to the limited literature on the use of repetitive transcranial magnetic stimulation in children and adolescents and illustrate the concept of using functional neuroimaging results to target the application of a focal intervention in an attempt to dampen hyperactive regions of the cortex.

Zh Vyssh Nerv Deiat Im I P Pavlova. 2005 Mar-Apr;55(2):202-6.

[Transcranial magnetic stimulation in research of emotion in the healthy and patients with epilepsy]

[Article in Russian]

Gimranov RF, **Kurdiukova EN**.

The main aim of this work was by using transcranial magnetic stimulation to investigate mechanisms of interhemispheric organization the emotion in the healthy and patients with epilepsy. The research was carried out on three groups: the first and second groups of healthy and third group of the patients with idiopatical epilepsy. The first and third groups received transcranial magnetic stimulation on right and left frontalis area. The second group was control (sham transcranial magnetic stimulation). Is shown, that transcranial magnetic stimulation of right frontalis area increases the examining time on negative photos and decreases on positive photos. Transcranial magnetic stimulation of left frontalis area in the healthy and patients with epilepsy increases the examining time on positive photos and decreases on negative photos. The right hemisphere at the healthy and patients with epilepsy in the greater degree is connected to negative marks of emotions, and left hemisphere with positive marks of emotions.

Child Adolesc Psychiatr Clin N Am. 2005 Jan;14(1):1-19, v.

Emerging brain-based interventions for children and adolescents: overview and clinical perspective.

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Electroencephalogram biofeedback (EBF), repetitive transcranial magnetic stimulation (rTMS), and vagal nerve stimulation (VNS) are emerging interventions that attempt to directly impact brain function through neurostimulation and neurofeedback mechanisms. This article provides a brief overview of each of these techniques, summarizes the relevant research findings, and examines the implications of this research for practice standards based on the guidelines for recommending evidence based treatments as developed by the American Academy of Child and Adolescent Psychiatry for attention deficit hyperactivity disorder (ADHD). EBF meets the "Clinical Guidelines" standard for ADHD, seizure disorders, anxiety, depression, and traumatic brain injury. VNS meets this same standard for treatment of refractory epilepsy and meets the lower "Options" standard for several other disorders. rTMS meets the standard for "Clinical Guidelines" for bipolar disorder, unipolar disorder, and schizophrenia. Several conditions are discussed regarding the use of evidence based thinking related to these emerging interventions and future directions.

Clin Neurophysiol. 2004 Dec;115(12):2728-37.

Seizure incidence during single- and paired-pulse transcranial magnetic stimulation (TMS) in individuals with epilepsy.

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OBJECTIVE: We reviewed published data and our own data to determine a quantitative incidence of seizure in subjects with epilepsy undergoing single- and paired-pulse transcranial magnetic stimulation (spTMS and ppTMS) and to explore conditions that may increase this risk. METHODS: A PubMed literature search was performed, and articles from this search were reviewed. Subjects from our institution also were included. RESULTS: The crude risk of a TMS-associated seizure ranges from 0.0 to 2.8% for spTMS and 0.0-3.6% for ppTMS. Medically intractable epilepsy and lowering antiepileptic drugs were associated with increased incidence. There was significant center-to-center variability that could not be explained by differences in patient population or by differences in reported stimulation parameters. In all cases, seizures were similar to each subject's typical seizure and without long-term adverse outcome. In

most cases, doubt was expressed in the original reports as to whether the seizures were induced by TMS or merely coincidental. CONCLUSIONS: The incidence of seizure in a subject with epilepsy during spTMS and ppTMS appears to be small and not associated with long-term adverse outcome. The incidence is higher under the specific conditions mentioned above. SIGNIFICANCE: These findings may enable researchers to more accurately inform subjects of seizure risk during TMS.

Rev Bras Psiquiatr. 2004 Jun;26(2):131-4. Epub 2004 Oct 27.

[Transcranial magnetic stimulation: review of accidental seizures]

[Article in Portuguese]

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Transcranial magnetic stimulation (TMS) is a new technique that has been used for the treatment of neuropsychiatric disorders, specially depression. It uses a magnetic stimulator that generates a magnetic field that is applied over the patient's skull with a coil. Possible seizures may be induced accidentally by TMS. TMS is usually used with sub threshold stimuli and seizures may occur by chance, especially when over the safety parameters. This article reviews the eight cases of undesirable seizures occurred with rTMS The possible mechanisms of seizure induction and the patients profile with a higher risk of convulsion are also described.

J Neurol Sci. 2004 Oct 15;225(1-2):157-60.

Epilepsia partialis continua as an isolated manifestation of motor cortical dysplasia.

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Cortical dysplasia has been increasingly recognized as a cause of epilepsy. We describe herein a 31-year-old female patient with epilepsia partialis continua (EPC) in the right extremities, which had lasted for 15 years without generalized seizures and other neurological deteriorations. MRI showed a focal thickening around the left motor area, indicative of cortical dysplasia, with adjacent subcortical abnormal T2 high intensity, suggestive of dysmyelination. Transcranial magnetic stimulation revealed low motor thresholds and markedly prolonged latencies of motor-evoked potentials (MEP) of the affected side, consistent with hyperexcitability of the cortical motoneurons accompanied by dysmyelination. This case demonstrates that motor cortex dysplasia can result in a

mild and non-progressive form of epilepsia partialis continua, associated with the characteristic MRI and MEP abnormalities.

Mult Scler. 2004 Aug;10(4):475-6.

Transcranial magnetic stimulation as a provocation for epileptic seizures in multiple sclerosis.

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Epileptic seizures may be of a provoked origin in acute phases of multiple sclerosis (MS), while chronic epilepsy typically occurs in advanced stages of the disease. A case of seizure provocation during diagnostic transcranial magnetic stimulation (TMS) is described here with a corresponding central nervous system (CNS) lesion in cranial magnetic resonance imaging. A subsequent chronic epileptogenesis originating from the opposite cerebral hemisphere was observed without further TMS influence after several years. The case in its clinical rarity demonstrates that standard single pulse TMS may trigger epileptic seizures only under limited conditions. Single pulse TMS is still regarded a safe procedure in MS.

Rinsho Shinkeigaku. 2003 Nov;43(11):799-801.

[Current diagnosis and treatment of status epilepticus]

[Article in Japanese]

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We reviewed the current diagnosis and treatment of status epilepticus (SE). The SE is defined as the condition in which a seizure persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur. Until recently, the most popular duration of seizures qualifying as SE has been 30 min. Nonetheless some clinicians suggest that the duration of the seizures that qualifies the SE should be shorter. In clinical settings the diagnosis of SE could be difficult without EEGs in patients who have complex partial SE or subtle SE, as their manifestation is coma without apparent motor sings. Pseudo-SE (psychogenic seizures) should be included in the differential diagnosis. Antiepileptic treatment should be administered immediately according to the protocol once the diagnosis of SE is made. In patients with refractory SE, general anesthesia with propofol or midazolam is recommended. Repetitive transcranial magnetic stimulation to the brain is effective for the treatment of SE in experimental animals, however further studies are necessary for clinical use.

Arq Neuropsiquiatr. 2004 Mar;62(1):21-5. Epub 2004 Apr 28.

Experimental therapy of epilepsy with transcranial magnetic stimulation: lack of additional benefit with prolonged treatment.

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OBJECTIVE: To investigate the effect of three months of low-frequency repetitive transcranial magnetic stimulation (rTMS) treatment in intractable epilepsy. METHODS: Five patients (four males, one female; ages 6 to 50 years), were enrolled in the study; their epilepsy could not be controlled by medical treatment and surgery was not indicated. rTMS was performed twice a week for three months; patients kept records of seizure frequency for an equal period of time before, during, and after rTMS sessions. rTMS was delivered to the vertex with a round coil, at an intensity 5% below motor threshold. During rTMS sessions, 100 stimuli (five series of 20 stimuli, with one-minute intervals between series) were delivered at a frequency of 0.3 Hz. RESULTS: Mean daily number of seizures (MDNS) decreased in three patients and increased in two during rTMS--one of these was treated for only one month; the best result was achieved in a patient with focal cortical dysplasia (reduction of 43.09% in MDNS). In the whole patient group, there was a significant ($p<0.01$) decrease in MDNS of 22.8%. CONCLUSION: Although prolonged rTMS treatment is safe and moderately decreases MDNS in a group of patients with intractable epilepsy, individual patient responses were mostly subtle and clinical relevance of this method is probably low. Our data suggest, however, that patients with focal cortical lesions may indeed benefit from this novel treatment. Further studies should concentrate on that patient subgroup.

Clin EEG Neurosci. 2004 Jan;35(1):4-13.

Current status of the utilization of antiepileptic treatments in mood, anxiety and aggression: drugs and devices.

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Interventions that have been utilized to control seizures in people with epilepsy have been employed by the psychiatric community to treat a variety of disorders. The purpose of this review will be to give an overview of the most prominent uses of antiepileptic drugs (AEDs) and devices like the Vagus Nerve Stimulator (VNS) and Transcranial Magnetic Stimulation (TMS) in the treatment of psychiatric disease states. By far, the most prevalent use of these interventions is in the treatment of mood disorders. AEDs have become a mainstay in the effective treatment of Bipolar Affective Disorder (BAD). The U.S. Food and Drug Administration has approved the use of valproic acid for acute

mania, and lamotrigine for BAD maintenance therapy. AEDs are also effectively employed in the treatment of anxiety and aggressive disorders. Finally, VNS and TMS are emerging as possibly useful tools in the treatment of more refractory depressive illness.

Zh Nevrol Psikhiatr Im S S Korsakova. 2004;104(3):25-31.

[Clinical and neurophysiological aspects of epilepsy with photosensitivity]

[Article in Russian]

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Using mapping EEG with dipole source location, transcranial magnetic stimulation (TMS), and visual evoked potential (VEP), clinico-neurophysiological analysis of photosensitivity was carried out in 7 patients with different types of epilepsy. In all the patients, an increase of visual response amplitude in VEP assessment and location of photogenic and eye-closing spike activity was observed in parietal and occipital areas that suggested a significant role of the striate and para striate cortex, along with primary projection cortex, in photosensitivity. Although motor cortex excitability by TMS causes hypersynchronization of the background activity and increase of slow wave discharge on the EEG after TMS. TMS is supposed to cause an activation of antiepileptic system.

Acta Neurol Scand. 2004 Apr;109(4):290-6.

rTMS reduces focal brain hyperperfusion in two patients with EPC.

Graff-Guerrero A, **Gonzales-Olvera J**, **Ruiz-Garcia M**, **Avila-Ordonez U**, **Vaugier V**, **Garcia-Reyna JC**.

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OBJECTIVE: This study was performed to evaluate the acute effect of a single repetitive transcranial magnetic stimulation (rTMS) session in a focal hyperperfusion epileptogenic region to induce a transitory decrease of epileptiform activity. CASE REPORT: Two epilepsia partialis continua (EPC)-diagnosed patients, received one session with 15 trains of rTMS (20 Hz; 2 s train, inter-train of 58 s). Before rTMS session, a brain ictal single photon emission computed tomography (SPECT) was performed to localize the focal frontal hyperperfusion region to establish the stimulation site. Immediately after the rTMS session another ictal SPECT was performed. Both patients showed a decrease of perfusion in the stimulated regions. For patient 1 epileptic seizures became intermittent until they stopped in the following 24 h. Patient 2 showed only a minimal improvement with a frequency decrease of epileptic spikes. CONCLUSIONS: Our findings suggest that a single rTMS session reduces focal epileptogenic activity and could be an

alternative approach for epileptic-resistant patients, but efficacy should be confirmed in a larger series.

Rev Neurol. 2004 Feb 16-29;38(4):374-80.

[Transcranial magnetic stimulation. Applications in cognitive neuroscience]

[Article in Spanish]

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OBJECTIVE: In this review we trace some of the mayor developments in the use of transcranial magnetic stimulation (TMS) as a technique for the investigation of cognitive neuroscience. Technical aspects of the magnetic stimulation are also reviewed. DEVELOPMENT: Among the many methods now available for studying activity of the human brain, magnetic stimulation is the only technique that allows us to interfere actively with human brain function. At the same time it provides a high degree of spatial and temporal resolution. Standard TMS applications (central motor conduction time, threshold and amplitude of motor evoked potentials) allow the evaluation of the motor conduction in the central nervous system and more complex TMS applications (paired pulse stimulation, silent period) permit study the mechanisms of diseases causing changes in the excitability of cortical areas. These techniques also allow investigation into motor disorder, epilepsy, cognitive function and psychiatric disorders. CONCLUSIONS: Transcranial magnetic stimulation applications have an important place among the investigative tools to study cognitive functions and neurological and psychiatric disorders. Even so, despite the many published research and clinical studies, a systematic study about the possible diagnostic value and role in neurocognitive rehabilitation of TMS testing need to be realized to offer new possibilities of future applications.

Lancet Neurol. 2004 Feb;3(2):111-8.

Brain stimulation for epilepsy.

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Neural stimulation is a promising new technology for the treatment of medically-intractable seizures. Vagus-nerve stimulation (VNS) is licensed in several countries as an adjunctive therapy. VNS is as effective as antiepileptic drug therapy, and serious complications are rare. Transcranial magnetic stimulation is simple, non-invasive, and

widely used in neurophysiology. Therapeutic results in a few studies are equivocal at best. Deep brain stimulation, although experimental, has been applied to the cerebellum, caudate nucleus, centromedian thalamus, anterior thalamus, subthalamus, hippocampus, and neocortical seizure foci. Preliminary results are encouraging, but not conclusive. Electrode implantation in the brain for indications other than seizures has been associated with a 5% risk for intracranial haemorrhage and 5% for infection. A controlled study of anterior thalamic stimulation in patients with intractable partial and secondarily generalised seizures has been started. Future investigations are likely to study extrathalamic sites of stimulation, and effects of stimulation contingent upon detection of or prediction of EEG patterns of epileptiform activity.

J Pharmacol Exp Ther. 2004 Apr;309(1):1-7. Epub 2004 Jan 16.

Brain stimulation for neurological and psychiatric disorders, current status and future direction.

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Interest in brain stimulation therapies has been rejuvenated over the last decade and brain stimulation therapy has become an alternative treatment for many neurological and psychiatric disorders, including Parkinson's disease (PD), dystonia, pain, epilepsy, depression, and schizophrenia. The effects of brain stimulation on PD are well described, and this treatment has been widely used for such conditions worldwide. Treatments for other conditions are still in experimental stages and large-scale, well controlled studies are needed to refine the treatment procedures. In the treatment of intractable brain disorders, brain stimulation, especially transcranial magnetic stimulation (TMS), is an attractive alternative to surgical lesioning as it is relatively safe, reversible, and flexible. Brain stimulation, delivered either via deeply implanted electrodes or from a surface-mounted transcranial magnetic device, can alter abnormal neural circuits underlying brain disorders. The neural mechanisms mediating the beneficial effects of brain stimulation, however, are poorly understood. Conflicting theories and experimental data have been presented. It seems that the action of stimulation on brain circuitry is not limited to simple excitation or inhibition. Alterations of neural firing patterns and long-term effects on neurotransmitter and receptor systems may also play important roles in the therapeutic effects of brain stimulation. Future research on both the basic and clinical fronts will deepen our understanding of how brain stimulation works. Real-time computation of neural activity allows for integration of brain stimulation signals into ongoing neural processing. In this way abnormal circuit activity can be adjusted by optimal therapeutic brain stimulation paradigms.

Neurosci Lett. 2004 Jan 9;354(2):91-4.

Intracranial measurement of current densities induced by transcranial

magnetic stimulation in the human brain.

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Transcranial magnetic stimulation (TMS) is a non-invasive technique that uses the principle of electromagnetic induction to generate currents in the brain via pulsed magnetic fields. The magnitude of such induced currents is unknown. In this study we measured the TMS induced current densities in a patient with implanted depth electrodes for epilepsy monitoring. A maximum current density of 12 microA/cm2 was recorded at a depth of 1 cm from scalp surface with the optimum stimulation orientation used in the experiment and an intensity of 7% of the maximal stimulator output. During TMS we recorded relative current variations under different stimulating coil orientations and at different points in the subject's brain. The results were in accordance with current theoretical models. The induced currents decayed with distance form the coil and varied with alterations in coil orientations. These results provide novel insight into the physical and neurophysiological processes of TMS.

Epilepsia. 2004 Jan;45(1):77-80.

Motor responses to afferent stimulation in juvenile myoclonic epilepsy.

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PURPOSE: To document whether the mechanisms responsible for myoclonic jerks in juvenile myoclonic epilepsy (JME) are similar to those causing other forms of myoclonus. METHODS: We studied somatosensory evoked potentials, the conditioning effect of cutaneous afferents on motor potentials evoked by transcranial magnetic stimulation (TMS), and intracortical inhibition and facilitation in response to paired TMS in a group of nine patients with JME and 20 normal controls. RESULTS: Intracortical inhibition was abnormal, whereas cortical somatosensory evoked potentials and TMS conditioned by cutaneous afferents were unaltered in JME patients. CONCLUSIONS: Abnormal processing of cutaneous afferents would not appear to contribute to myoclonus in JME.

J Neurosci. 2003 Nov 26;23(34):10867-72.

Priming stimulation enhances the depressant effect of low-frequency repetitive transcranial magnetic stimulation.

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Low-frequency (1 Hz) repetitive transcranial magnetic stimulation (rTMS) can depress the excitability of the cortex locally and has been proposed for the treatment of disorders such as schizophrenia and epilepsy. Some have speculated that the depressant effect is related to long-term depression (LTD) of cortical synapses. Because in vitro LTD can be enhanced by pretreatment of synapses with higher-frequency stimulation, we hypothesized that if rTMS depression had mechanisms in common with LTD, higher-frequency priming would increase it also. In 25 healthy volunteers in two experiments, we measured motor-evoked potentials (MEPs) from TMS of the motor cortex to define the baseline response. Subthreshold rTMS (6 Hz, fixed rate or frequency modulated) was used to prime the motor cortex, followed by suprathreshold 1 Hz stimulation for 10 min at just above the MEP threshold. Over the next 60 min, we recorded MEPs every 10 sec and found significant increases in the amount of cortical depression with both types of 6 Hz priming rTMS relative to sham. The MEP depression from 6 Hz-primed 1 Hz rTMS showed no evidence of decay after 60 min. Pretreatment with 6 Hz primes both 1 Hz rTMS depression and LTD. Although not conclusive evidence, this strengthens the case for overlapping mechanisms and suggests a potent new technique for enhancing low-frequency rTMS depression that may have experimental and clinical applications.

Epilepsy Behav. 2003 Oct;4 Suppl 3:S46-54.

Treatment of depression in patients with epilepsy: problems, pitfalls, and some solutions.

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Many people with epilepsy suffer from comorbid depression. Despite this, there have been few studies addressing the treatment of depression in this population, and the literature on psychiatric management techniques in patients with epilepsy is composed largely of opinions rather than evidence from randomized, controlled trials or other systematic investigations. Antidepressant drugs, including tricyclics and selective serotonin reuptake inhibitors, can be used to treat patients with epilepsy and comorbid depression. Nonpharmacological treatment options include vagus nerve stimulation, transcranial magnetic stimulation, and psychological therapies including cognitive-behavioral therapy, individual or group psychotherapy, patient support groups, family therapy, and counseling. Another important area that remains largely uninvestigated is psychiatric research in patients with epilepsy in non-Western cultures (with the exception of Japan). Factors such as problems with access to and acceptability of therapies in many

developing nations have further implications for the treatment of psychiatric disorders in epilepsy.

Neurosci Lett. 2003 Nov 6;351(1):9-12.

Anti-kindling effect of slow repetitive transcranial magnetic stimulation in rats.

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The cerebrospinal fluid (CSF) of animals exposed to electroconvulsive shock (ECS) has anticonvulsant properties when injected into naive animals. The present study investigated whether the CSF of humans exposed to 1 or 10 Hz repetitive transcranial magnetic stimulation (rTMS) has similar properties. Using a 4 day rat flurothyl kindling seizure model we found that the kindling rate was significantly decreased by intraventricular injection of CSF from depressed patients exposed to 1 Hz rTMS. The CSF from patients that underwent 10 Hz rTMS showed a trend toward an increased kindling rate. These results support the similarity of ECS and rTMS and suggest that 1 Hz and 10 Hz rTMS produce distinct physiologic changes.

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Suprathreshold 0.3 Hz repetitive TMS prolongs the cortical silent period: potential implications for therapeutic trials in epilepsy.

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OBJECTIVE: To investigate the after-effects of 0.3 Hz repetitive transcranial magnetic stimulation (rTMS) on excitatory and inhibitory mechanisms at the primary motor cortex level, as tested by single-pulse TMS variables. METHODS: In 9 healthy subjects, we studied a wide set of neurophysiological and behavioral variables from the first dorsal interosseous before (Baseline), immediately after (Post 1), and 90 min after (Post 2) the end of a 30 min long train of 0.3 Hz rTMS delivered at an intensity of 115% resting motor threshold (RMT). Variables under investigation were: maximal M wave, F wave, and peripheral silent period after ulnar nerve stimulation; RMT, amplitude and stimulus-response curve of the motor evoked potential (MEP), and cortical silent period (CSP) following TMS; finger-tapping speed. RESULTS: The CSP was consistently lengthened

at both Post 1 and Post 2 compared with Baseline. The other variables did not change significantly. CONCLUSIONS: These findings suggest that suprathreshold 0.3 Hz rTMS produces a relatively long-lasting enhancement of the inhibitory mechanisms responsible for the CSP. These effects differ from those, previously reported, of 0.9-1 Hz rTMS, which reduces the excitability of the circuits underlying the MEP and does not affect the CSP. This provides rationale for sham-controlled trials aiming to assess the therapeutic potential of 0.3 Hz rTMS in epilepsy.

Seizure. 2003 Sep;12(6):373-8.

Usefulness of magnetic motor evoked potentials in the surgical treatment of hemiplegic patients with intractable epilepsy.

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Five hemiplegic patients with intractable epilepsy were studied with transcranial magnetic stimulation (TMS) before and after various surgical treatments. These patients had unilateral widespread cerebral lesions acquired at various times, including congenital, infantile and childhood injury. Motor evoked potentials (MEPs) of the abductor pollicis brevis (APB) muscles were simultaneously recorded on both sides following TMS of the motor cortex in the respective hemisphere using a figure-8 or circular coil. In all patients with congenital disease, the abolition of motor function in the affected hemisphere was estimated by magnetic MEPs, and the hemiplegia did not deteriorate after functional hemispherectomy (HS) was performed in two of them. In two patients with acquired disease, HS was not performed because it was shown by magnetic maps that the motor function in the affected hemisphere remained. Furthermore, it was shown by electric MEPs using subdural electrodes that a patient who had had encephalitis in early childhood had a reorganised motor area in the parietal cortex of the affected hemisphere. The present findings indicate that magnetic MEPs are a very useful non-invasive method of assessing whether the motor area in the affected hemisphere can be resected in hemiplegic patients with intractable epilepsy.

Nervenarzt. 2003 Aug;74(8):664-76.

[Electric brain stimulation for epilepsy therapy]

[Article in German]

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Attempts to control epileptic seizures by electrical brain stimulation have been performed for 50 years. Many different stimulation targets and methods have been investigated. Vagal nerve stimulation (VNS) is now approved for the treatment of refractory epilepsies by several governmental authorities in Europe and North America. However, it is mainly used as a palliative method when patients do not respond to medical treatment and epilepsy surgery is not possible. Numerous studies of the effect of deep brain stimulation (DBS) on epileptic seizures have been performed and almost invariably report remarkable success. However, a limited number of controlled studies failed to show a significant effect. Repetitive transcranial magnetic stimulation (rTMS) also was effective in open studies, and controlled studies are now being carried out. In addition, several uncontrolled reports describe successful treatment of refractory status epilepticus with electroconvulsive therapy (ECT). In summary, with the targets and stimulation parameters investigated so far, the effects of electrical brain stimulation on seizure frequency have been moderate at best. In the animal laboratory, we are now testing high-intensity, low-frequency stimulation of white matter tracts directly connected to the epileptogenic zone (e.g., fornix, corpus callosum) as a new methodology to increase the efficacy of DBS ("overdrive method").

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Attenuation of epilepsy with application of external magnetic fields: a case report.

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We have previously demonstrated that magnetoencephalographic (MEG) brain measurements in patients with seizure disorders show significant MEG activity often in the absence of conventional EEG abnormalities. We localized foci of seizure activity using the mapping technique characterized by the ISO-Spectral Amplitude (ISO-SA) on the scalp distribution of specified spectral components or frequency bands of the emitted MEG Fourier power spectrum. In addition, using an electronic device, we utilized the above recorded activity to emit back the same intensity and frequency of magnetic field to the presumed epileptic foci. Using this method we were able, over the past two and one-half years, successfully to attenuate seizure activity in a cohort of over 150 patients with various forms of epilepsy. We present a patient with severe epilepsy and behavioral disturbances in whom application of an external artificial magnetic field of low intensity produced a substantial attenuation of seizure frequency which coincided with an improvement in the patient's behavior. This case demonstrates that artificial magnetic treatment may be a valuable adjunctive procedure in the management of epilepsy.