Transcranial Magnetic Stimulation and Its Applications in Children

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Transcranial magnetic stimulation (TMS) provides a non-invasive method of induction of focal currents in the brain as well as transient modulation of the function of the targeted cortex. TMS is now widely used as a diagnostic tool in adults. In children, its application to date has been limited, even though TMS offers unique opportunities to gain insights into the neurophysiology of a child's brain. Using the single-pulse TMS technique, investigators can measure motor thresholds, motor evoked potentials, silent periods, central conduction times, and the paired-pulse curve to study central nervous system development and central motor reorganization after a cerebral lesion. Repetitive TMS (rTMS) is a novel treatment for psychiatric illness that is undergoing trials for a range of disorders in adults. Although there are rare published data on rTMS as a treatment for neuropsychiatric diseases in young persons, the benefits from TMS are nevertheless encouraging. Two important issues of pediatric TMS are safety considerations and methodology. In the future, rTMS may play an important role in the study and possibly in the therapy of children's diseases after more safety studies are completed. *(Chang Gung Med J 2002;25:424-36)*

Key words: transcranial magnetic stimulation, children's brains, central motor reorganization.

For sensory afferent pathways, evoked potentials have been fully studied with respect to their changes with maturation of the central nervous system (CNS), but for corticospinal motor pathways, electrophysiological examinations in children have been limited by the methodology.[1] Clinical examination is sometimes unreliable particularly in the very young child.[2] Transcranial magnetic stimulation (TMS) provides the opportunity to objectively assess the integrity of corticospinal tracts in children.[3] TMS can non-invasively induce motor evoked potentials (MEPs) in extremity muscles, and do so more safely and painlessly than with high-voltage electrical stimulation of the brain.[4,5] TMS has the potential not only for evaluating the maturity of the corticospinal motor pathways in normal children, but also of becoming a routine diagnostic procedure in children with motor developmental delay or other disorders of motor control.

Since the introduction in 1985 by Barker et al.[4,6] of a compact coil stimulator, single-pulse TMS has become an invaluable tool for evaluating the human motor system in health and disease.[7,8] The development of devices capable of stimulation at frequencies of up to 60 Hz has greatly expanded the applicability of TMS to the study of higher cognitive functions. Unlike other techniques for cortical stimulation, TMS can be used in the study of normal subjects and patients with a variety of neuropsychiatric conditions rather than being restricted to patients undergoing neurosurgical procedures for medically intractable epilepsy or focal brain lesions. Applied

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as single pulses appropriately delivered in time and space or in trains of repetitive stimuli at appropriate frequencies and intensities, TMS can be used to transiently disrupt the function of a given cortical target, thus creating a temporary "virtual brain lesion". This allows the study of the contribution of a given cortical region to a specific behavior.[9]

TMS can be used to complement other methods in the study of central motor pathways,[10] the evaluation of corticocortical excitability,[11,12] and the mapping of cortical brain functions.[13] In addition, TMS provides a unique methodology for determining the true functional significance of the results of neuroimaging studies and causal relationships between focal brain activity and behavior.[9]

Physiological background

There are 4 main components in a magnetic stimulator, including (1) the power supply, (2) storage capacitors, (3) switching elements, and (4) coil. Magnetic stimulation represents a form of "electrodeless" stimulation in which the generated magnetic field bridges the gap between primary and secondary currents.

Currently available magnetic stimulators can be classified according to the delivered current pulses into (1) biphasic current pulse stimulators (Cadwell MES-10 stimulator), (2) monophasic current pulse stimulators (Magstim or Dantec stimulators), and (3) polyphasic current pulse stimulators (Magstim Super Rapid or Dantec Magpro). Since the direction of current flow determines which neural elements are activated within the cortex, a biphasic pulse may stimulate a greater number of different populations of cells than would a monophasic pulse.[14] The maximal magnetic field generated is around 2 Tesla (T) for most devices. Magnetic stimulating coils that are circular induce a maximal stimulating current in an annulus underneath the coil. Many conventional coils are 8-10 cm in diameter, which means that a considerable volume of brain tissue can be activated. However, for the purpose of TMS studies in children, smaller coils can be manufactured. In order to increase the focality of stimulation, coils are often wound in a figure 8 shape where the magnetic field at the center of the 8 is twice that at the 2 wings. At low to moderate intensities of stimulation, activation can be considered to occur only at the junction region of the figure 8 (Fig. 1).

General applications

Four basic ways of applying TMS to the study of human cortical physiology and the physiological correlates of cognitive functions are discussed.

1. TMS as a brain mapping tool

Focal TMS can be applied in single pulses or short trains of repetitive stimuli to differential scalp positions, thus targeting different brain regions. The simplest possible application of TMS in this context is to register the effects induced by TMS depending on the part of the brain being stimulated. When TMS is applied sequentially to scalp positions distributed on a grid, a map of a given brain region can be generated. Another way of using TMS for mapping purposes is to give subjects a task and study how TMS disrupts task performance depending on the site of stimulation.[15,16] Anatomic correlation of the results of TMS studies can be achieved by identifying the position of the magnetic stimulation coil and the calculated site of intersection of the evoked magnetic field with the subject's brain cortex on the subject's 3D-rendered magnetic resonance images (MRIs). The subject's head can be digitized along with the position of the TMS coil on the scalp and the digitized points co-registered onto the subject's MRI. A frameless, image-guided stereotactic system can be adapted to allow precise, on-line anatomical localization of the coil placement and the presumed stimulated site on the subject's brain.[17,18]

2. TMS as a probe of neural networks

TMS can be applied at variable intervals following a given stimulus, thus providing information about the temporal profile of activation and about data processing along elements of neural networks. In this fashion, TMS can be used to evaluate the functional significance of elements of a neural network in a given task, thus enhancing the information derived from neuroimaging studies, or it can be combined with neuroimaging studies to demonstrate the functional connectivity between cortical areas.[19,20] This technique can be used to study mechanisms of neural plasticity as well.[21]

3. TMS as a measure of cortical excitability

Since TMS mostly activates cortical neurons transynaptically, its effects are highly dependent on cortical excitability. The study of different measures

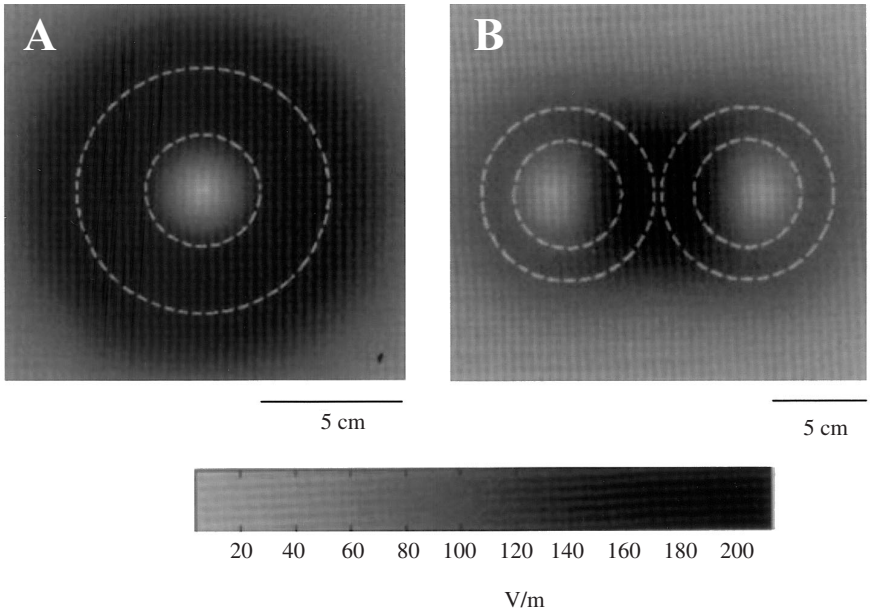

Fig. 1 Distribution of an induced electric field by (a) a circular and (b) a figure-8 stimulating coil. The circular coil has a 41.5-mm inside turn diameter, a 91.5-mm outside turn diameter, a 66.5-mm mean diameter, and 15 turns of copper wire. The figure-8 coil has a 56-mm inside turn diameter, a 90-mm outside turn diameter, a 73-mm mean diameter, and 9 turns of copper wire per winding. The outline of both coils is depicted with dashed white lines on a representation of the calculated plane 20 mm below a realistic model of the coil ($dI/dt = 108\ A\ S^{-1}$). (Modified from figures created by A. Barker in ref. 5).

of cortical excitability can provide insights into neurotransmitter modulation underlying different pathologies, cognitive functions, and plastic reorganization of cortical networks during brain development, maturation, rehabilitation, and learning.

Four parameters are used to measure cortical excitability and their presumed underlying mechanisms: (a) the motor threshold (MT), (b) paired-pulse curve, (c) cortical silent period (CSP), and (d) input-output curve.

4. TMS as a modulator of brain function

Depending on the stimulation frequency and intensity, TMS can enhance or decrease cortical excitability in a more-sustained fashion following the application of repetitive TMS (rTMS) trains.[22,23] Such studies of rTMS might provide important insights into the pathophysiology of depression,[24-26] obsessive compulsive disorder, Parkinson's disease, dystonia, myoclonic epilepsy, and a variety of other neuropsychiatric disorders.[27-31] This modulation of cortical excitability beyond the duration of the rTMS train itself raises the possibility of exploring potential therapeutic uses of rTMS.[32] For the most part, data are very preliminary to date. However, sufficient evidence has accrued to conclude that rTMS (particularly at frequencies of > 5 Hz applied to the left dorsolateral prefrontal cortex) exerts antidepressant effects over and beyond placebo contributions.[32,33] The beneficial effects seem to last for days, weeks, and possibly even months.[32,34]

Diagnostic applications in children

In 1988, Koh and Eyre reported for the first time the successful application of TMS in a study of maturation of corticospinal tracts in children.[35] They studied 142 subjects who ranged in age from 33 weeks of gestation to 50 years.[35] To record muscle action potentials, skin-mounted electromyographic (EMG) electrodes were placed over the right abductor digiti minini in all subjects older than 6 months of age; in those aged less than 6 months the muscle action potential was recorded from the right biceps brachii. The latency from cortical stimulation to the

onset of the evoked muscle action potential was determined; a subject's standing height, or crown to heel length in those less than 1 year old, was also recorded.[35] Since then, TMS has become a valuable tool in the field of pediatric neurophysiology. However, methodological issues are essential considerations in assessment studies that have employed TMS to investigate corticospinal projections in children.

Koh et al. measured latencies from the cortex to target muscles in the upper extremities but did not separately stimulate spinal cord or nerve roots in order to work out true central motor conduction times.[35] They obtained responses even in preterm babies, using various preinnervational strategies. Their data therefore might be confounded by latency variations due to different preinnervational levels. It has been shown that interference with voluntary motor activity changes the latency of responses to motor cortex TMS for up to 3 ms in normal adults.[36-38] In addition, preinnervational levels are very difficult to control systematically in children. Therefore, great care needs to be taken to ensure that subjects are quiet and relaxed, or alternatively a set amount of passive stretching needs to be applied.

Of course, difficulties in using TMS in children are greatest in "restless" subjects. Muller et al. described a difficult subject "...a mentally retarded 3-year-old child with cerebral palsy, who presented with marked spasticity of all 4 extremities and athetotic movements in the upper extremities. In this child, who was neither able to stay quiet nor to follow instructions, different levels of preinnervation gave rise to a change in latency at the right thenar by up to 8 msec." Muller et al. concluded that interpreting latencies is difficult unless the examination is restricted to a relaxed state. Latency variability even in normal children is much more marked than in adults.[39] In cooperative children, Heinen induced action-phase EMGs by asking children to perform an aimed grip using an elastic spring coil-loaded device.[40,41]

TMS has allowed clinicians to more precisely investigate maturation of the central motor system and corticospinal pathways in healthy children. The TMS parameters of motor system excitability, namely resting and active MTs, cortical silent period, and intracortical inhibition and facilitation, represent different CNS mechanisms; and these mechanisms may have different developmental courses.[42]

Motor threshold (MT)

MT intensity for TMS is determined as greater than 100% stimulator output intensity in children aged 1 year or less. With increasing age, MT declines until it reaches the adult level at 13 to 16 years (46.5% + 6.6%).[1,42-44] For excitation of cervical motor roots, MT intensity falls rapidly over the first 2 years and then matches adult values.[43] The higher MTs in young children may indicate a hypoexcitability of motor system neuronal membranes. Threshold intensities for TMS may be less useful in children younger than 10 years, because of their higher mean values and variability between individuals.[1]

Motor evoked potentials (MEPs)

The reproducibility of MEPs elicited by TMS is markedly dependent on the degree to which stimulus intensity exceeds the threshold intensity as well as the state of the target muscle. In addition, it is of course critical whether or not the TMS coil is positioned over the optimal scalp site.[45] In order to obtain comparable MEPs in children, investigators have generally adjusted the stimulus intensity to an intensity of 10% above MT intensity, and MEPs have been recorded from a resting target muscle.[1] However, as mentioned above, this methodology can be difficult to implement. First, MT can be impossible to determine in children aged below 18 months to 2 years.[1,36] Some investigators have even reported a failure to evoke MEPs reliably below the age of 6 years.[35,43] Furthermore, as discussed above, establishing a relaxed status of the target muscle in children can be extremely complicated and unreliable.

MEPs are generally polyphasic in early childhood and gradually become triphasic with age. The mean amplitude of MEPs is less than 500 μV with little change at between 1 and 9 years, but it tends to increase between 10 years and adulthood. The duration of MEPs, which is not influenced by age, is less than 16 ms over the ages studied.[1]

Central conduction time (CCT)

CCT can be calculated by subtracting the conduction time in peripheral nerves from the total latency of MEPs, with both being measured at the onset of the initial deflection (Fig. 2). Koh et al. first

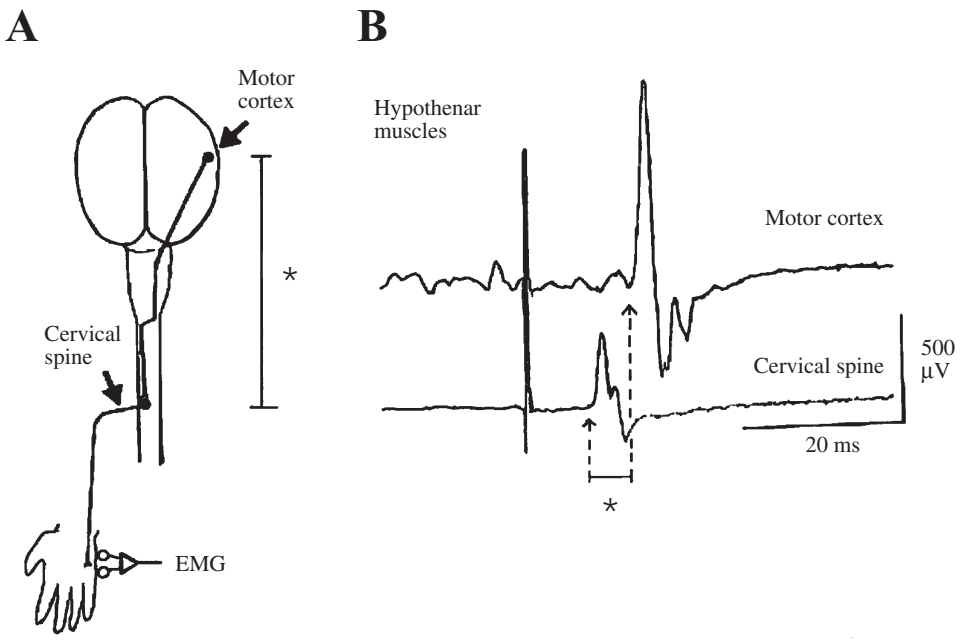

Fig. 2 Motor evoked potentials obtained in single trials from a subjects aged 12 years. A, Experimental protocol; B, sample records. The upper record shows the response to stimulation of the motor cortex and the lower record the response to stimulation over the cervical roots. Central conduction time (*) is calculated by subtracting the conduction time in peripheral nerves from the total latency of MEPs, both measured at the onset of initial deflection. (Modified from figures by Eyre et al., J Physiol, 1991)

showed a progressive increase in central motor conduction velocity within the descending motor pathways up to the age of 11 when adult values are achieved.[35] Muller et al. showed that motor conduction times of the peripheral nervous system do not change significantly beyond the age of about 3-4 years, and that the decrease in CCT lasts up to the of about 10 years before adult values are reached.[36,39] Muller et al. used TMS to show, for the first time, that the development of the fastest voluntary movements is a structure-bound phenomenon, and is independent of learning.[39]

It is important to emphasize again that preinnervation conditions (relaxed or facilitated) profoundly affect the CCT. The CCT after TMS not only reflects the conduction time along the axon but also includes the synaptic transmission and depolarization times of the neurons at both the cortical and the spinal ends.[41] In children, the facilitated CCT was similar to that of adults at approximately 3 years of age.[43,46] However, the relaxed CCT in children did not match that in adults until about 10 years.[36] It has been proposed that the facilitated CCT could be an early established functional parameter of the motor system, allowing the motor cortex to access spinal motoneurons with a constant delay.[43] It has been speculated that the relaxed CCT correlates with morphologic maturation, in particular with myelination of fast corticospinal tract fibers.[36] In a study by Heinen et al., the facilitated CTT of children aged 6 to 9 years was similar to that of adults. However, for the relaxed CTT, the latency jump and stimulus intensity differed between children and adults. Heinen et al. concluded that at an early school age, children already possess mature fast corticospinal pathways able to access spinal motoneurons through the pyramidal tract. However, despite the partial adult-like level of neuronal maturation, young school children were not able to perform deliberate motor actions with the same proficiency as could adults.[41]

Cortical silent period (CSP) and transcallosal inhibition (TI)

The CSP is thought to be caused by an intracor-

tical inhibitory mechanism in the stimulated hemisphere.[47] In adults, the CSP can be easily evoked by TMS. Heinen et al. demonstrated that in children aged 4.2 to 5.7 years, the duration of the CSP is significantly shorter, lasting about 75% of that detected in adults.[40] Moll et al. showed that the duration of the CSP increased with increasing age.[42] However, study of the CSP requires maintenance of a set amount of voluntary contractions of the target muscle. As discussed above, this is difficult in children, so this technique is difficult to apply in young or restless children.

By applying TMS with a figure-8 coil, it is possible to reliably restrict the effects of stimulation to 1 hemisphere. The stimulus can suppress ongoing voluntary EMG activity in an ipsilateral distal muscle. This inhibition, called transcallosal inhibition (TI), is most likely due to activation of callosal fibers, which pass through the anterior half of the trunk of the corpus callosum and connect both primary motor cortices.[48] The absence of TIs in children implies that cortical synaptic organization of the immature brain does not permit inhibition of contralateral motoneurons via interhemispheric transfer (Fig. 3).[40] Maturation of functionally active callosal connections appears to occur after the age of 5 years. On the other hand, no ipsilateral MEPs could be detected after the age of 10 years. This disappearance of ipsilateral corticospinal responses was explained by increased transcallosal inhibitory influences during motor system development.[40,42,46]

Intracortical inhibition and facilitation

Deficient motor system inhibitory mechanisms may be closely related to uncontrolled behavior in childhood neuropsychiatric disorders, but to date, the significance of developmental aspects is unclear.[42] As discussed above, intracortical inhibition and facilitation produced by a subthreshold conditioning stimulus in a paired-stimulus TMS paradigm are thought to be due to activation of inhibitory or facilitatory interneuronal circuits in the motor cortex.[49] The overall aspect of intracortical excitability curves of healthy children, aged from 8 to 16 years, is comparable to that of excitability curves of adults (Fig. 4).[42,44] At short interstimulus intervals (2-4

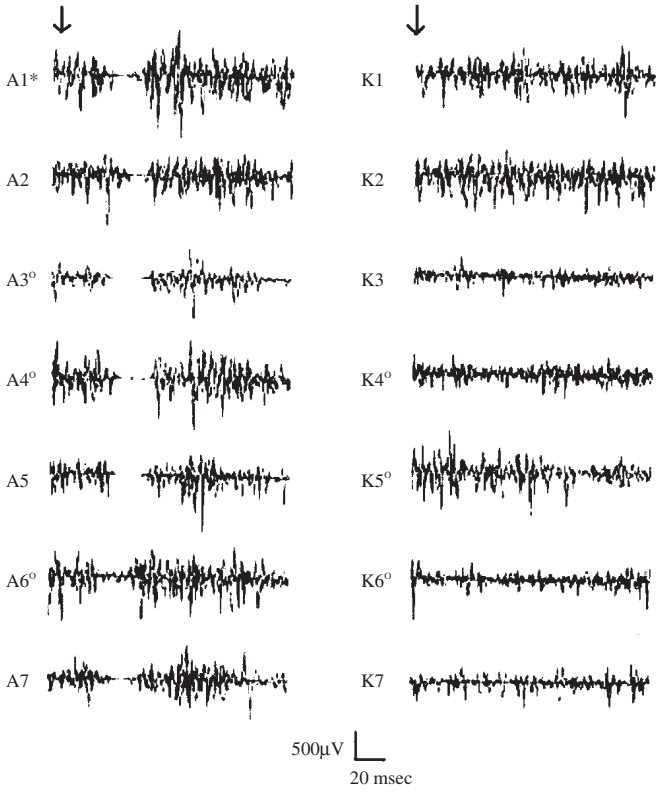

Fig. 3 Ipsilateral responses of adults (A1-7) and children (K1-7) shown as 4 superimposed trace recordings under the conditions of facilitation. Whereas all adults had transcallosal inhibition, there were no ipsilateral responses in the children. The display of amplitude gain is 500 (V/div, which had to be adapted for 5 individuals. *=1 mV/div; ¡ C=200 µV/div. The stimulus was applied at the time indicated by arrows. (Reprinted from ref. 40 with permission from J Wiley & Sons)

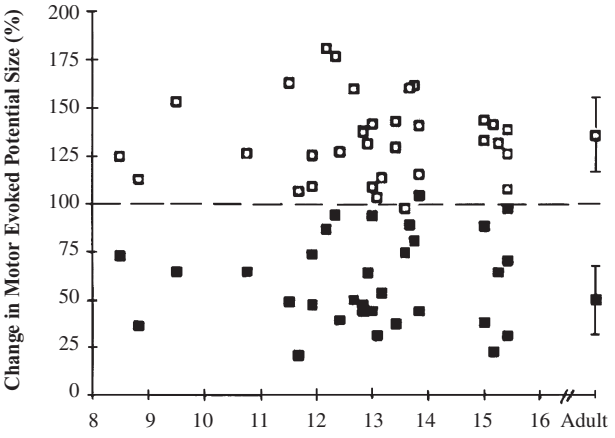

Fig. 4 Scatter plot of intracortical inhibition (mean value across inhibitory interstimulus intervals of 2-4 ms) vs. age (¡), and intracortical facilitation (mean value across facilitatory interstimulus intervals of 7-20 ms) vs. age (¡), respectively. Mean (¡ SD) adult values for comparison. (Reprinted from ref. 42 with permission from Elsevier Science)

ms), a conditioning stimulus produces inhibition of the test response, while facilitation of the test response occurs at longer intervals (7-10 ms). No age-dependent changes have been found, for either inhibitory or facilitatory interstimulus intervals.[42] This can be explained by assuming that intracortical facilitation and MT are complementary phenomena of motor system excitability with fundamental differences.[49]

TMS and motor disturbances in children

In children with central motor disturbances, evidence of abnormalities in motor system excitability can be demonstrated by TMS. A variety of conditions have been studied to date. For example, prolonged latencies between the motor cortex and target muscles (prolonged CCT) have been reported in children with hemiparesis.[39] The CCT has been found to be shortened in children with Rett's syndrome.[50,51] In children with tic disorders, MT was normal,[52] while the CSP was significantly shortened compared to healthy controls; this did not depend on tic localization. Using the paired-pulse technique, intracortical inhibition and facilitation were shown not to differ between tic disorder children and healthy children.[52] Increased MT, prolonged latency of MEP, and slowing of the CCT have been found in children with multiple sclerosis.[53] In children with attention-deficit hyperactivity disorder (ADHD), motor hyperactivity is one of the striking abnormalities. Using TMS, Moll et al. showed that there is evidence for inhibitory deficits within the motor cortex in ADHD children and for an enhancement of inhibitory mechanisms in this brain region by methylphenidate.[54]

It is well known that functional recovery is quite good in patients with early hemisphere lesions compared to those with lesions acquired later.[55] It has been postulated that the ipsilateral motor cortex can compensate for motor representation of the affected limbs.[56] TMS can be used to provide evidence of central motor reorganization in children with cerebral palsy.[57-59] Ipsilateral hand motor responses to TMS are not usually elicited in normal adult subjects, but are frequently observed in patients with early brain lesions, especially congenital lesions.[57,58,60-62] The cortical motor representation area for the tibialis anterior muscle has been reported to be located more laterally, toward the area of representation for the arm muscles, in spastic patients with preterm birth, but not in spastic patients with full-term birth or in athetoid patients.[58] However, further studies on normal development are needed in order to fully establish the significance of such findings. For example, it is still unclear how many young children might have ipsilateral responses to TMS or at which age such responses might be considered pathological. As documented by Wassermann et al., some ipsilateral MEPs, even in hand muscles, can be evoked in normal adult volunteers.

Therapeutic applications in children

TMS is a novel treatment for psychiatric illness that is undergoing trials for a range of disorders in adults. Unfortunately, there are rare published data on TMS as a treatment for neuropsychiatric diseases in young persons.[63] We are aware of only 3 published studies in which rTMS was applied to children. Wedegaertner et al. reported the application of 1-Hz rTMS at 110% of MT intensity for 30 min to the motor cortex of 3 children with action myoclonus.[64] Tormos et al. (unpubl. data) applied the same rTMS schedule to 3 children with progressive myoclonic epilepsy. In both studies, rTMS decreased myoclonic activity, but resulted in no further clinical or behavioral changes in the children.

Using formal pooling through the TMS Listserver (tms_info@pupk.unibe.ch), an email exchange of worldwide users and investigators in the field of TMS supported by the International Society for Transcranial Stimulation (ISTS), Walter collected information from investigators who had used TMS in patients 18 years or younger.[63] Data on 7 teenage patients treated at the Laboratory for Magnetic Brain Stimulation at Beth Israel Deaconess Medical Center and Harvard Medical School were compiled. These young patients had participated in 1 of 3 TMS trials, a trial on bipolar disorder, another on unipolar recurrent medication-refractory major depression, and a third on schizophrenia. The average age was 17.4 years. Different rTMS parameters were applied, and improvement occurred by conclusion of the TMS course in 5 of the cases. Most importantly, adverse events were reported in only 1 patient and consisted of a mild muscle-tension headache that was promptly resolved with treatment.

Preliminary data from such a small number of children should not be over-interpreted, but the benefits from TMS are nevertheless encouraging.[63] More results from medical centers, larger case series, and, eventually, controlled trials of TMS in children are needed before definite conclusions can be drawn.

Safety issues

In adults, most of the safety concerns raised by TMS are limited to rTMS. Single-pulse TMS has essentially no known harmful side effects in adults, and it seems reasonable to assume a similar safety margin in children. On the other hand, the limited experience and reluctance among TMS researchers to study the use of rTMS in children are understandable. Therapeutic applications of rTMS are experimental and largely only supported by preliminary pilot data. Furthermore, the safety of rTMS in children and adolescent needs to be systematically evaluated before conducting further studies. The studies must emphasize safety monitoring, including neurophysiologic, neuropsychologic, audiologic, and hormonal functions.[63] Safety guidelines, similar to those published for the use of rTMS in adults, need to be developed for the application of rTMS in children.

Contraindications for rTMS

Metallic hardware near the stimulation coil can be moved or heated by TMS. Thus, the presence of metal anywhere in the head, excluding the mouth, is generally a contraindication. Individuals with cardiac pacemakers and implanted medication pumps, an intracardiac line, or severe cardiac disease should also be excluded from the studies. In most studies, patients with epilepsy, a past history or a family history of seizures, and patients with brain lesions who may have a lower seizure threshold should be excluded. Furthermore, pregnant women should be excluded because of the risk of fetal damage in the event of a TMS-induced seizure.

Tricyclic antidepressants, neuroleptic agents, and other drugs that lower the seizure threshold are contraindications for rTMS, except in extraordinary circumstances where the potential benefit outweighs the increased risk of a seizure.[31,65]

Histotoxicity

Concern that TMS may harm the developing brain is an important issue in children. Although no published data have focused on the histotoxicity of TMS on the developing brain, there have been no reported adverse events in children.[35-43] The electrical energy generated by TMS has been estimated to be 0.05%-0.005% of that applied in a burst of electroconvulsive therapy;[5] the peak magnetic field of 2.0 T induced by TMS yields a maximum charge density of approximately 0.94 $\mu C/cm^2$/phase in tissue, which is markedly below the minimum level of 40 $\mu C/cm^2$/phase at which evidence of neural damage has been found with stimulation at 50 Hz.[66] No microscopic damage in the brain was recognized in 31 rats given 10,000 stimuli of 3.4 T or in 16 infant rabbits given 1000 stimuli of 2.0 T.[67, 68] Two adult patients with intractable seizures who received 1000-1200 stimuli prior to a temporal lobectomy also showed no organic damage to the target temporal cortex.[69] Concerning the effect on local neuronal activity and changes in blood flow within the cerebral cortex, TMS does not impairs electroencephalographic activity, cerebral flow, blood pressure, heart rate, or prolactin secretion.[70,71]

Accidental seizures

Single-pulse TMS has produced secondarily generalized or partial motor seizures in several patients with lesions of the CNS such as strokes.[72,73] However, single- and paired-pulse TMS can be con-

sidered to be free of the risk of seizure induction in normal volunteers and patients without conditions predisposing them to epilepsy. Nevertheless, clinicians should pay close attention when TMS is applied in children aged from 6 months to 5 years that are at high risk of febrile seizures. There is no evidence to suggest that a single provoked seizure or even a series of induced seizures, as seen in electroconvulsive therapy for depression, makes another seizure more likely in an otherwise healthy individual.

Neuropsychological and motor effects

Although several studies have examined the transient effects of focal rTMS on various cognitive, perceptual, or other functions, very few have considered longer-lasting, unintended effects of extended exposure. A subsequent safety study examining the effects of exposure to rTMS of 1 and 25 Hz at an intensity above MT, delivered to multiple scalp positions in the same subjects, similarly failed to document any significant undesirable complications.[74] Varying effects on cognitive, perceptual, and motor functions have been observed. These include finger tapping, improved verbal memory, dysphoria, and euphoria.[75] Because of the risk of such cognitive and motor side effects, subjects should undergo detailed neuropsychological testing and quantitative motor evaluation before and serially following rTMS.

Effect on hearing

Transient threshold shifts and tinnitus have been reported in animals and humans. These effects are thought to be secondary to the intense click produced by the rapid mechanical deformation of the stimulating coil when it is energized. The use of foam earplugs has been demonstrated to prevent this risk and should be obligatory for all subjects undergoing TMS and rTMS studies.[65]

Local pain and headaches

Local pain and headaches can be induced by rTMS due to direct activation of muscles and nerves near the stimulation coil on the scalp. This is rarely a problem following single- or paired-pulse TMS. The discomfort appears to be related to both the intensity and frequency of the stimulation. According to the experience of many different investigators, the incidence of these headaches may reach 15% or 20%, but these headaches have always responded well to mild analgesics, such as acetaminophen.[75]

Scalp burns from electrodes

Eddy currents induced in metal surface EEG electrodes located near a stimulating coil can cause them to heat up, and a skin burn may have been observed on 1 occasion.[76] This risk is associated with rTMS but does not pertain to single- or paired-pulse TMS. Heating is related to the size and conductivity of the electrode as well as the stimulation parameters. In this context, special consideration should be given to the small size of a child's head and brain which may contribute to changes in the charge density induced by TMS.

Kindling

Kindling is a process whereby the repeated administration of an initially subconvulsive stimulus results in progressive intensification of induced neuroelectrical activity, culminating in a seizure. Classic kindling occurs most effectively in the range around 60 Hz, and generally requires pulse durations of 1 ms. While it is of theoretical concern, there is no evidence for it in practice.[31] However, there is no doubt that in this context, as in regard to other, long-term theoretical complications of rTMS, children may be at a particularly high risk due to their developing brain and much higher degree of plasticity. Therefore, particular care and careful safety studies are required.

Summary

TMS represents a relatively new field of clinical neurophysiology which is undergoing rapid evolution. The method is clinically suitable and extremely useful for determining propagation and excitability characteristics of central motor tracts and along the proximal portions of spinal roots and nerves. Single-pulse stimulation has been applied in the past decade for the study of children with no complications reported. Compared to healthy adults, higher motor thresholds and shorter cortical silent periods have been reported in healthy children. Two important issues of pediatric TMS are safety considerations and methodology. rTMS may have significant therapeutic applications for a variety of neuropsychiatric dis-

eases in the future. However, until more is known about the potential deleterious effects of rTMS on the development of the CNS, young children should not be allowed to serve as subjects in rTMS studies without compelling clinical reasons.

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穿顱腦磁激術及其兒童的應用

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穿顱腦磁激術 (transcranial magnetic stimulation，TMS) 提供一種非侵入性的方法，可以在腦部誘發局部興奮電位，而且可以在腦皮質造成短暫性的功能變化。利用這種方法，在成人方面已經廣泛地當成神經生理學的診斷工具，並利用它做神經行爲及神經精神方面的研究。對於小孩子，雖然目前應用上還是有所限制，但已經提供一個特殊的機會來探索兒童腦部的神經生理學。利用單一脈衝穿顱腦磁激術 (single pulse TMS)，我們可以測量腦部運動閾值 (motor threshold)、中樞傳導時間 (central conduction time)、肌肉運動興奮電位 (motor evoked potential)、靜止期 (silent period)、成對脈衝刺激曲線 (paired-pulse curve)，以獲得更多兒童腦部生理的資訊；並可發現腦部發展過程及受傷後中樞運動神經重新組織的證據。再經過更多安全性的了解，高頻率連續性穿顱腦磁激術 (repetitive TMS) 將來在兒童神經學上所扮演的角色也可能像在成人領域方面一樣重要。(長庚醫誌 2002;25:424-36)

關鍵字：穿顱腦磁激術，兒童腦部，中樞運動神經重新組織。

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