Transcranial Magnetic Stimulation – New Modality in Brain Mapping

a report by
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Dr Risto J Ilmoniemi is currently working at the Helsinki University Central Hospital, where he is Head of the BioMag Laboratory, which belongs to the Helsinki Brain Research Center (HBRC), a Centre of Excellence of the Academy of Finland. Sharing the goal of HBRC to better understand the operation of the human brain, his research interests include biomagnetic technology and the inverse problem, evoked magnetic fields, spontaneous brain activity and transcranial magnetic stimulation (TMS). His work on TMS has led to the development of stereotactic TMS combined with high-resolution electroencephalography (EEG). Dr Ilmoniemi is also founder and Chairman of the Board of Nexstim Ltd, which will introduce a new generation of computer-assisted, stereotactic TMS combined with EEG in 2002. He developed biomagnetic theory and technology in the Low Temperature Laboratory of the Helsinki University of Technology (HUT) from 1978 to 1993 and at New York University from 1985 to 1987. In 1992, he was appointed Docent of Neurophysics at HUT. Dr Ilmoniemi received his MSc and PhD in Physics from HUT in 1981 and 1985, respectively.

The human brain can be stimulated non-invasively by strong magnetic field pulses that induce a flow of current in the tissue, leading to the excitation of neurons. Known as transcranial magnetic stimulation (TMS), this technique has grown dramatically in popularity since its initial demonstration by Barker, et al., in Sheffield, England, in 1985.

Until now, most TMS experiments and applications have been limited to the stimulation of the motor cortex because the only observable effects of magnetic stimulation have been those reflected in muscular activity. For example, when the hand representation area of the motor cortex is stimulated, contralateral fingers may be observed to twitch, provided that the neural pathway is intact. In the past few years, however, it has been demonstrated that the cortical effects of TMS can also be observed directly, for example, by means of electroencephalography (EEG), positron emission tomography (PET) or functional magnetic resonance imaging (fMRI).

With TMS, it is possible to:

- measure cortical excitability;
- study the integrity and efficacy of area-to-area connections;
- disturb on-going neuronal signal processing in the brain in order to find cortical areas that are important for specific tasks; and
- treat patients by targeting repetitive stimulation into specific cortical areas.

Many variations and combinations of these paradigms are possible.

Several modern imaging techniques such as magnetoencephalography (MEG) or fMRI are able to reveal the function of the human brain *in vivo*. TMS is different from these in the sense that, instead of observing the brain in operation, neurons are triggered into action. It is expected that TMS, in particular in combination with EEG or other functional brain mapping techniques, will have wide applications both in basic research and in clinical applications, including diagnosis and therapy.

The Technology

The field strength of up to several tesla required in magnetic brain stimulation is achieved by discharging a capacitor so that a strong current pulse passes through a coil placed over the scalp. No contact to the head needs to be established; the scalp and the skull have virtually no effect on the magnetic field. The effect in the brain is due to the movement of ions induced by the changing magnetic field and the consequent depolarisation of cell membranes.

The field intensities achieved in TMS are lower than or equal to the field in a typical modern MRI scanner. There is no reason to believe that the effect of the magnetic field of a brief pulse would be any more harmful than a static one, which itself appears to pose no danger. Power dissipation due to TMS is also low; the total dissipated power in the brain during 20Hz repetitive TMS (rTMS) is less than 1mW, i.e. several orders of magnitude less than the brain's metabolic power of some 20W. After over a decade of intense scrutiny, TMS seems to be considered a safe technique. A comprehensive report on the safe use of TMS was presented by Wassermann.

The focus of stimulation depends on the type of coil and on its distance from the head; small coils pressed against the scalp generally producing the most confined stimulation. In early magnetic stimulators, only circular coils were used; better focus can be obtained with the figure-of-eight coil. In the future, the brain can be stimulated by means of superposed fields from an array of dozens of small coils in a helmet-like arrangement. The current amplitude in the coils will be controlled individually, which makes it possible to move the stimulated spot electronically without moving the coils themselves.

Stereotactic TMS

In traditional TMS studies, the coil is placed over the head by using external landmarks or by trial and error until the desired response (for example, thumb twitch) is generated. By contrast, in stereotactic TMS, the coil is positioned over the target location on the basis of individual MRI images of the brain so that the anatomical feature of the brain that is stimulated can be defined.

Stereotactic TMS (see *Figure 1*) allows precise determination of the dose applied to different cortical areas, which is not possible with standard equipment. In a stereotactic system, the level of the induced field may be selected instead of the stimulus amplitude as a percentage of the maximum stimulator output or on the basis of the individual motor threshold or cortical response. The better control of stimulus parameters made possible by the new generation of instruments will improve reliability and safety as well as allow the definition of precise guidelines for magnetic stimulation.

TMS Combined with EEG

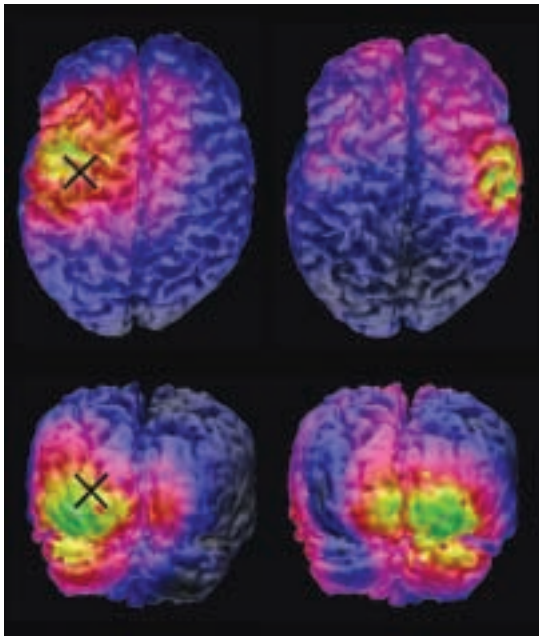
TMS and multichannel EEG were first combined by Ilmoniemi, et al., (see *Figure 2*). In previous attempts, the saturation of EEG amplifiers had made it impractical to record EEG during the first tens of milliseconds after the stimulus.

The system consists of a specially designed 60-channel EEG amplifier and a cap with C-shaped electrodes, allowing artefact-free data to be obtained just milliseconds after TMS pulses are delivered to the brain.

Figure 1: The TMS-EEG System

The stereotactic computer-controlled TMS-EEG system developed at the BioMag Laboratory of the Helsinki University Central Hospital allows the measurement of cortical reactivity and functional connectivity. The stimulator coil can be moved to target brain areas on the basis of individual anatomical brain images (MRI).

Figure 2: Activation Time Sequences Obtained by HIgh-resolution EEG after TMS to the Left Sensorimotor Cortex (Upper Row) and to the Posterior Cortex (Lower Row)



The initial ipsilateral activation (left) is followed by contralateral activation (right).[5]

The main advantage of concurrent TMS and EEG is the possibility of studying cortical excitability and functional connectivity on a millisecond scale. Ilmoniemi, et al., determined and followed the spreading of activity on the basis of cortically constrained current-density estimates calculated from potential maps. The study by Komssi, et al., (in press) indicated that combined TMS and EEG can reveal transcallosal conduction times with an accuracy of one millisecond.

TMS Combined with PET and fMRI

Paus, et al., combined TMS and PET, introducing a new technique permitting the mapping of neural connections in the living human brain. While stimulating a selected cortical area, they measured changes simultaneously in cerebral blood flow. The exact location of the stimulation site was achieved by frameless stereotaxy. They found significant correlations between cerebral blood flow and the number of TMS pulse trains, demonstrating functional connectivity from the left frontal eye field to visual areas in the superior parietal and medial parieto-occipital cortex.

The use of TMS within MRI equipment is not straightforward due to the magnetic forces between the two systems and because the TMS coil and the currents it contains may distort the MRI images. Nevertheless, it has been demonstrated recently that TMS-evoked brain activation can be measured by using fMRI.

Temporary Lesions

A powerful TMS paradigm was introduced by Amassian, et al. They demonstrated that a subject's performance in a character identification task was impaired when single magnetic pulses were administered between 60ms and 140ms after the onset of the visual stimulus. A temporary functional lesion had been created artificially.

The temporary-lesion paradigm has been used subsequently in a variety of experiments. For example, Pascual-Leone, et al., showed that, by applying rTMS to language areas in the dominant hemisphere, speech production can be arrested. In certain cases, this procedure may replace the risky and costly Wada test, which is used to determine the hemisphere that is speech-dominant prior to surgery, which may affect speech production.

Pharmacological Studies

Ziemann, et al., studied the effects of epileptic drugs on motor cortex excitability using TMS, opening the way to a promising new paradigm. Kähkönen, et al., used the combination of TMS and high-resolution EEG to measure how ethanol changes TMS-evoked cortical activity.

Stimulating the motor cortex in the left hemisphere, they observed alcohol-induced changes not only in the stimulated area, but also in the frontal cortex, including the contralateral hemisphere. It appeared that ethanol had changed the functional connectivity between motor and prefrontal cortices.

With pharmaceutical studies utilising TMS-evoked responses, new kinds of information of cellular-level mechanisms *in vivo* can be obtained and the effects of drugs on cortical excitability and functional connectivity in individual patients can be assessed objectively. This promises to be a major application of TMS in basic research and in drug testing.

Clinical Potential of TMS

Since the invention of TMS, single-pulse TMS has been utilised in the evaluation of central and peripheral motor pathways. In practice, the most important field has been the examination of central motor pathways in conditions where the conduction times are known or suspected to be lengthened.

In particular, the evaluation of central versus peripheral motor function is utilised for differential diagnostics in disorders involving the spinal motor system such as amyotrophic lateral sclerosis, in trauma and in some cases of stroke.

An interesting addition in the future may be the evaluation of not only spinal, but also intracerebral functional connections in degenerative disorders utilising simultaneous TMS and EEG.

TMS is used increasingly for depression therapy. George, et al., treated medication-resistant depressed patients by applying rTMS to the left dorsolateral prefrontal cortex, where neuronal activity appears to be lowered in depression. After daily sessions of treatment for at least five days, two out of six subjects showed significant mood improvement. Several other authors (for example, Pascual-Leone, et al.) have subsequently reported positive results on depressed patients as well as on other patient groups but it is still too early to draw final conclusions on the efficacy of TMS therapy. In any case, there is hope that rTMS may replace the inconvenient electroconvulsive therapy at least in some cases of drug-resistant depression.

rTMS has also been an experimental treatment for patients with obsessive-compulsive disorders, post-traumatic stress, schizophrenia and Parkinson's disease. However, the physiological mechanisms underlying the effects and the conclusive demonstration of the efficacy of rTMS in depression therapy, as well as in the treatment of other neuropsychiatric disorders, still requires extensive clinical trials.

Conclusion

In its 16 years of existence, TMS has evolved into a valuable technique for both clinicians and basic researchers. It is a unique and powerful tool, providing a means to examine cortical excitability and connectivity in normal and abnormal human brains *in vivo*. On the other hand, rTMS has shown promise as an alternative treatment in several psychiatric disorders, in particular, depression. In cognitive neuroscience, the excellent temporal resolution of TMS is invaluable in determining brain-behaviour relations with, for example, temporary lesion studies. Advances in precise targeting of TMS, improved techniques for the recording of TMS-evoked activity, integration with MRI and other imaging techniques and new experimental paradigms and clinical applications promise a bright future for TMS. ■

Additional Information

The complete version of this article, including references, can be found in the Reference Library on the CD-ROM accompanying this business briefing.