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Exploring brain circuitry: Simultaneous application of Transcranial Magnetic Stimulation and functional Magnetic Resonance Imaging

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1. Introduction

Transcranial magnetic stimulation (TMS) has proven invaluable as a technique for stimulating specific brain areas; such local stimulation induces changes in cortical excitability, and modifies specific cognitive functions. Hence, it affords a good measure of a variety of parameters, including neural conduction and processing time, activation thresholds, and facilitation and inhibition in the brain's cortex, so supporting the exploration of human motor- and visual-systems, and cognition. This technique has been widely used as a research tool to investigate the brain's plasticity, response to emotions, and cognition. It also has been used as a clinical tool to study some neurological diseases, such as epilepsy, and often as a treatment tool in alleviating psychiatric disorders, and for hastening recovery of motor function after stroke.

Functional magnetic resonance imaging (fMRI), based on Blood Oxygenation Level Dependence (BOLD) contrast, is one of the commonest neuroimaging techniques. The preference for this imaging modality rests upon its ability to "record", non-invasively, neuronal activity when the human brain is involved in specific tasks. Furthermore, because it carries low risk or none, and lacks side effects, experiments can be repeated and verified. Due to these advantages, BOLD-fMRI has been used in studies that involve healthy populations, people with diseases, and those using drugs, to explore the brain activity during primary and higher cognitive/behavioral tasks, using a variety of different paradigms, to evaluate attention, memory, language processing, and decision-making.

These two techniques have been widely used in neuroscience, mainly because of their non-invasiveness and low risk factor; however, using them alone has revealed some limitations. For example, because the stimulation paradigms used in fMRI studies are complex, it is unclear whether or not a specific area is essential for a particular function; moreover, the resulting map of brain functional connectivity, based on cross-correlating the BOLD signal, is an indirect measurement and, hence, the direction of causality remains uncertain. Similarly, TMS rests on the implicit assumption that the applied magnetic pulse locally disrupts neural activity at the site of stimulation, inducing changes in the corresponding behavioral performance. However, recent TMS-fMRI studies indicated that the neural consequences of focal TMS are not restricted to the site of stimulation, but spread throughout different brain regions. Therefore, the only reliable way directly to assess the neural effects of a TMS stimulus is via the simultaneous combination of TMS and functional brain-imaging techniques. Particularly, the coincident TMS-fMRI combination allows us to stimulate brain circuits while simultaneously monitoring changes in its activity and behavior. Such an approach can help to identify brain networks of functional relevance, and support causal brain-behavior inferences across the entire brain. Undoubtedly, this approach promises to contribute majorly to cognitive neuroscience. However, the drawback to its universal adoption is the great technical challenge that this technique imposes, and, thus, few research groups routinely employ it.

In this chapter, I overview the principles underlying the fMRI and TMS techniques, discuss the general applications of each, and detail the safety issues related to using TMS. Thereafter, I describe the technical implementation of the TMS device inside the MRI scanners, and finally outline the current possibilities and limitations of this promising multimodality technique.

2. fMRI Overview

Basis

fMRI is a non-ionizing, non-invasive imaging technique that allows us to use information generated by the hemodynamic process to study brain function. Although the connection between neural activity and changes in blood flow and blood oxygenation in the human brain was known since the end of nineteen century (Roy, et al. 1890), it was only toward the end of the twentieth century that this phenomena started to be explored.

The hemodynamic response is defined as the dynamic regulation of the blood flow in the brain. Thus, when neurons perform some specific task, their consumption of oxygen increases and because they do not accumulate internal energy reserves, viz. glucose and oxygen, they require the rapid delivery of energy as they start firing. Consequently, after a delay of about 1–5 seconds, local blood flow increases and rises to a peak over 4–5 seconds before falling back to baseline (Raichle, et al. 2006); since this increase in blood supply exceeds the local increase in oxygen consumption, there is a local change in blood flow and oxygenation (Fox, et al. 1985).

Such changes induce temporary modifications in tissue permeability, so altering the MRI signal. Essentially, since hemoglobin is diamagnetic when oxygenated (oxyhemoglobin) but paramagnetic when deoxygenated (deoxihemoglobin) (Pauling, et al. 1936) the magnetic resonance (MR) signal of blood differs slightly, depending on the oxygenation level. More specifically, the effective transverse relaxation time (T_2*) increases in activated brain regions with decreased deoxyhemoglobin concentration (Ogawa, et al. 1990) that causes a local increase of the MRI signal (Fig. 1). This effect, called the blood oxygenation level dependence (BOLD) contrast, is the basis for most fMRI studies.

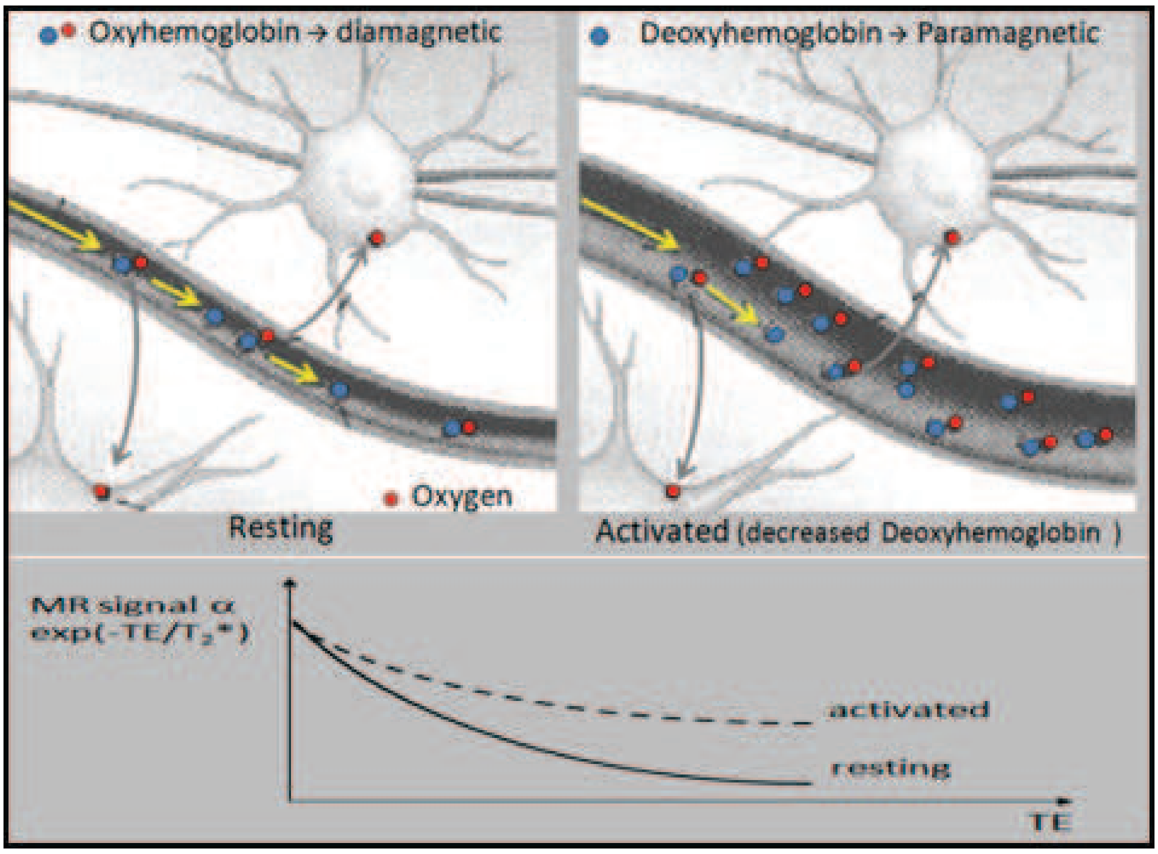

Fig. 1. Local activation versus resting in the brain.

Changes in BOLD contrast can be observed by collecting data in an MRI scanner with sequence parameters sensitive to changes in magnetic susceptibility, i.e., by using T_2* sensitive imaging and fast sequences, such as Echo Planar Imaging (EPI) (Bandettini, et al. 1992). These changes can be either positive or negative depending on the relative changes in both cerebral blood flow (CBF) and oxygen consumption. Increases in CBF that exceed changes in oxygen consumption will entail an increased BOLD signal (activation); conversely, decreases in CBF that surpass changes in oxygen consumption will engender a decreased one (deactivation). Since the BOLD contrast-to-noise ratio (CNR) increases with the static magnetic field (Gati, et al. 1997, Okada, et al. 2005) recent technical improvements, such as using high magnetic fields (van der Zwaag, et al. 2009) and multichannel RF reception (Pruessmann, et al. 1999), have advanced spatial resolution to the millimeter scale. Currently functional images are usually acquired every 1–4 seconds with a spatial resolution of 2–4 millimeters on each side of the cubic voxel.
Despite hardware and software improvements to increase the signal-to-noise ratio (SNR) the BOLD signal is still very small (typically 1–5%) (Caparelli, et al. 2003). Furthermore, because of the significant intra/inter subject variability, we cannot directly quantify fMRI results. Accordingly, the data must be evaluated statistically, which involves many

experimental repetitions of a thought, action, or experience to determine reliably which areas of the brain are activated/deactivated.

Data analysis: The goal of fMRI data analysis is to reveal correlations between brain activation and the task performed by a person during the scan. However, the BOLD signal is small, and other sources of noise in the acquired data, such as small head motion, and physiological noise, can mask the results; hence , the data must be corrected to eliminate these unwanted effects. Accordingly, after reconstructing the resulting series of 3D images of the brain, the output of the scanning session undergoes a series of steps starting with correction for motion. Following this, the data is normalized to put all the images in the same frame for a group analysis. This step puts all images for each subject into one standard format that is set by a template; finally spatial filtering is also performed. The final outcome is a time series of 3 D scanned volumes ready to be correlated with the used task voxel-by-voxel, which will produce a statistical map of task-dependent activation.

There are many software packages available for the statistical analysis of the fMRI data, such as, the Statistical Parametric Mapping (SPM) (Friston 1996), Analysis of Functional NeuroImages (AFNI) (Cox 1996), FMRIB Software Library (FSL) (Smith, et al. 2004), and most of them also offers the data pre-processing described above.

MRI Safety

Magnetic field: The static magnetic field, present in all MRI scanners (example fig. 2), is generated by the electrical currents that are always circulating the superconductor material that compose the MRI scanner tunnel; it is used to align the spin of all protons (^1H) by making them move around an axis along the direction of the field, thereby generating a net magnetization in the tissue. Although exposure of people to this magnetic field has not resulted in permanent biological damage, it may entail in them a transient dizziness (Chakeres, et al. 2005), vertigo (Glover, et al. 2007), and a metallic taste (Cavin, et al. 2007). This field can also interfere with the function of electromechanical devices, and attract any iron-containing (ferromagnetic) objects, making them move suddenly and with great force into the scanner, thereby posing in risk anyone who is in the projectile's (metallic "flying" object) path. The magnetic field can also exert a pull on any ferromagnetic object in the body, such as certain medication pumps or aneurysm clips, causing serious internal body damages.

Therefore, any object that is brought to the scanner room needs to be MRI-compatible while everyone who will be inside or at the vicinity of an MRI scanner, viz., staff , patients, and study volunteers, must undergo a careful screening to avoid any incident that could lead to serious injuries and sometimes, even to death.

Radio frequency (RF): RF pulses alter the alignment of the net magnetization, causing the hydrogen nuclei to produce a rotating electromagnetic field that the receiver coil at the MRI scanner can detect. This RF pulse can heat living tissue to the point of inducing hyperthermia in patients/research volunteers; therefore, to avoid this problem, the specific absorption rate (SAR) parameter was established that determines how much RF a specific body can tolerate safely according to tissue density. SAR is defined as the power absorbed per mass of tissue, usually averaged over a specific volume, so providing a measure of the rate of absorbed energy by the tissue, in watts per kilogram, when exposed to a RF electromagnetic field (Oh, et al. 2010).

Fig. 2. 4 Tesla MRI Varian scanner at Brookhaven National Laboratory (BNL)

RF can also heat some tattoo pigments, particularly those that contain trace metals and are frequently used for regular tattoos or tattooed eye-liner (permanent makeup), potentially causing skin burns (Stecco, et al. 2007, Wagle, et al. 2000)

Peripheral nerve stimulation (PNS): Magnetic field gradients encode the spatial position of the MR signal generating an MR image. Special coils designed to produce a linearly varying spatial dependence of the magnetic field along a particular axis create these gradients. Fast sequences, mainly those commonly employed for some imaging techniques, such as fMRI, and Diffusion Tensor Imaging (DTI), require these fields to be switched on and off quickly. However, such rapid switching can causing peripheral nerve stimulation, inducing symptoms from mild tingling and muscle twitching to a sensation of pain. Indeed, volunteers have reported a twitching sensation, particularly in their extremities, when exposed to rapidly switched fields. Therefore to avoid PNS incidents, regulatory $d\mathbf{B}/dt$ (change in field per unit time) limits were specified (Glover 2009).

Acoustic noise: The exchanges between the readout and phase encoding currents in the gradient coils under the main static magnetic field of the MR scanner induce Lorentz forces that act on the gradient coils. Accordingly, the coils and wires buckle and bend, inducing compression waves in the surrounding gradient supports; these motions are conducted toward the MR system's peripheral structures and launched into air as loud acoustic noises (clicking or beeping). Because the Lorentz forces increase logarithmically with the magnetic fields' strength and with the applied gradient current, the noise levels rise with both. During echo planar imaging (EPI) the equivalent-continuous sound pressure levels (SPLs) range from 90–117 dB, with a peak level up to 130 dB at 1.5 T; at 3.0T, they range from 105–133 dB with a peak level up to 140 db (Moelker, et al. 2003). Therefore, using appropriate ear protection, such as MRI-compatible sound-suppressor headphones and ear plugs, is essential for anyone inside the MRI scanner room.

fMRI: Pluses & Pitfalls

fMRI is a neuroimage technique that offers several advantages: it noninvasively records brain signals without risks of radiation inherent in other scanning methods, such as computed tomography (CT) or positron emission tomography (PET) scans; it has high spatial resolution (2–3 mm) and records signals from all regions of the brain, unlike electroencephalography (EEG) and magnetoencephalography (MEG) that are biased towards the cortical surface; and, BOLD-fMRI offers better spatial resolution than EEG and MEG, and has similar spatial- and better temporal-resolution than PET. fMRI is widely used to image brain "activation" and there are standard data-analysis approaches that allow researchers from different laboratories to compare results. Cross-correlations of BOLD signal changes in the brain have been used to indirectly map the functional connectivity in the brain, including the visual (Ogawa, et al. 1992), motor (Kim, et al. 1993), and language areas (Hinke, et al. 1993). Thus, BOLD-fMRI is used extensively to study brain connectivity in humans due to MRI's intrinsically low risks.

However, the indirectness of the fMRI connectivity measurements is a concern because the postulated interconnection pathways rely on biophysical models (Friston, et al. 2003). The lack of specificity on the direct association between the standard stimulus paradigm and the corresponding activated areas (1 cognitive function => 1 specific brain area) is another limitation in traditional fMRI studies. Pernet and colleagues recently reviewed this issue (Pernet, et al. 2007), underlining the need to use several cognitive processes to categorize objects (e.g., related to information encoding, attention, and memory); thus, a generic effect of categorization could easily pass as a brain correlate of category specificity. The solution for this non-specificity problem entails a difficult theoretical consideration, attaining the appropriate dimensionality of the design is practically unfeasible, since a true demonstration of category specificity would require exhaustively testing all possible interactions between categories and task properties. Therefore, brain activation patterns consistent with category specificity remain unidentified. In addition, a category-specificity effect is not localized to a given processing region; instead, it concerns the strength of functional connection from one area to another. Thus, as suggested by these authors, only by testing the effective connectivity, i.e., by measuring the influence that one neuronal system or cortical area exerts over another we can understand the processes at work in each module, and assert the process/information interaction. Finally, because of the complexity of the stimulation paradigms used in functional studies, frequently involving many brain regions and more than one basic function, it is unclear whether or not a specific area is essential for a particular function (Pernet, et al. 2007, Tomasi, et al. 2007). Therefore, since fMRI findings are always correlations, the direction of causality cannot be determined.

The precise relationship between neural signals and BOLD is actively researched. In general, changes in BOLD signal correlate well with changes in blood flow. In fact, the BOLD signal represents sophisticated convolution of changes in the cerebral metabolic rate of oxygen (CMRO2), the CBF, and cerebral blood volume (CBV) associated with focal neuronal activity (i.e., the energy consumption of the neuronal population); therefore, it indirectly

measures neuronal activity composed of CBF contributions from larger arteries and veins, smaller arterioles and venules, and capillaries. Experimental results indicate that the BOLD signal can be weighted to the smaller vessels, and hence, closer to the active neurons, by using alternative MRI techniques (Song, et al. 2003) or larger magnetic fields, since the size of the BOLD signal increases with the increase of the magnetic field's strength.
fMRI has poor temporal resolution because the BOLD response peaks approximately 5 seconds after neuronal firing begins in an area, and it is difficult to distinguish BOLD responses to different events that occur within a short time. Therefore, to overcome these drawbacks, some multimodalities are under development, such as combining fMRI signals having relatively high spatial resolution with signals recorded with other techniques, such as EEG or MEG with higher temporal resolution but worse spatial resolution.

3. Introduction to TMS

History of Transcranial Magnetic Stimulation
Even though Franz Mesmer, in the eighteen century, has proposed the use of magnets to cure disease, it was not until the end of nineteenth century that scientists started to use magnetic energy to alter brain activity. The first publications on magnetic stimulation described Jacques D'Arsonval's experiments in 1898 stimulating the retina, and similar work by Silvanus P. Thompson in 1910 (Thompson 1910); at that time, the magnetic stimulators were powerful enough to activate the retinal cells, causing the subjects to perceive light flashes, but the fields generated were too weak to stimulate brain tissue.
In 1965, Bickford and Fremming (Bickford, et al. 1965) used a damped 500 Hz sinusoidal magnetic field to demonstrate muscular stimulation in animals and humans. Subsequently, Oberg (1973) magnetically excited nerve tissue. Polson and colleagues, in 1982, reported the first successful magnetic stimulation of superficial nerves (Polson, et al. 1982). Finally, three years later, the first Transcranial magnetic stimulation of the central nervous system and cortical regions was achieved (Barker, et al. 1985). Neurologists quickly adopted Barker's device, and now routinely employ single-stimulus TMS instruments to measure nerve-conduction time. The therapeutic potential of TMS was unrealized until the repetitive stimulator (rTMS), which generates up to 30 pulses per second, became available in the 1990s.

Basis
TMS is based on the Faraday's principle of electromagnetic induction, wherein a pulse of current flowing through a coil of wire generates a magnetic field. According to the Biot-Savart law (Jackson 1965, Reitz, et al. 1993) when a electric current flows through a ferromagnetic material it generates a magnetic field that is perpendicular to the current's direction (Fig. 3). If this magnetic field varies with time, this field will induce a current in any conductive material nearby; the rate of change determines the size of the induced current (Faraday's law). Finally, by Lenz's law, this induced current always flows in a direction that will oppose the change in magnetic field causing it (Jackson 1965). This principle of electromagnetic induction describes how a brief, high-current magnetic pulse produced in a TMS coil induces a current on the brain region lying underneath the coil, resulting on the depolarization of the neurons (Hallett 2000, Sack, et al. 2003). However, the

current induced in the brain is not composed of free electrons but of the ions, which are responsible for tissue conductivity.

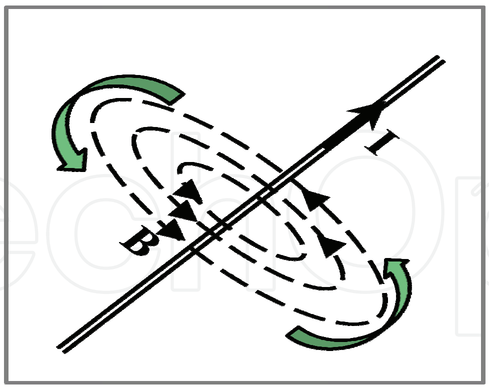

Fig. 3. Magnetic field lines, B, surrounding the current distribution, I,

TMS devices are made of two hardware components: a high-current pulse generator that produces discharge currents of about 5,000 amps (Figure 4 shows an example of the top-of-the- line instrument); and, a stimulating coil that generates magnetic pulses with field strengths of 1 -2 Tesla, and duration of 200 – 400 µs, depending on the coil shape/size. Fig 5a depicts the more traditional circular TMS coil shapes that produce pulses of high-intensity magnetic fields; however, they are not as focus as the figure-of-eight coil, shown in Fig. 5b, that can stimulate a region as small as 1 cm^2; however, this second coil shape is not as powerful as the circular coil (Anand, et al. 2002, Hallett 2000, Jalinouz 1998, Sack, et al. 2003). The pulses from coils shapes showed in Figure 5a and 5b can only penetrate the brain's cortical regions, about 1.5 cm beneath the scalp (Epstein, et al. 1990, Rudiak, et al. 1994, Wassermann 1998), but alternative shapes were developed, such as the double-cone coil, Fig. 5c, that was designed to stimulate brain structures down to 3 – 4 cm (Tada, et al. 1990).

Fig. 4. Magstim super-rapid² TMS device at BNL that can deliver pulses reaching up to 100 Hz.

The TMS device can apply different stimulus intensities; for some cognitive functions, we can associate intensity with the ability to induce, or not, a specific behavioral output, which can define the threshold. For the motor area, the threshold for a motor-evoked potential (MEP) statistically is defined as the lowest intensity of stimulus needed to induce thumb movement, or to trigger MEPs of 50 mV or more in the abductor pollicis brevis muscle (thumb abductor muscle) for at least 50% of the applied pulses (Rostrup, et al. 1996, Sack, et al. 2003). Another observable output induced by TMS stimulus is the phosphene sensation. This feeling is characterized by experiencing flashes of light without light actually entering the eye; TMS induces this sensation in some people when the stimulus is applied on the occipital area. Thus, the phosphene threshold is defines as the lower intensity needed to generate the visualization of phosphenes when the stimulus is applied in the occipital area for at least 50% of the applied pulses (Stewart, et al. 2001).

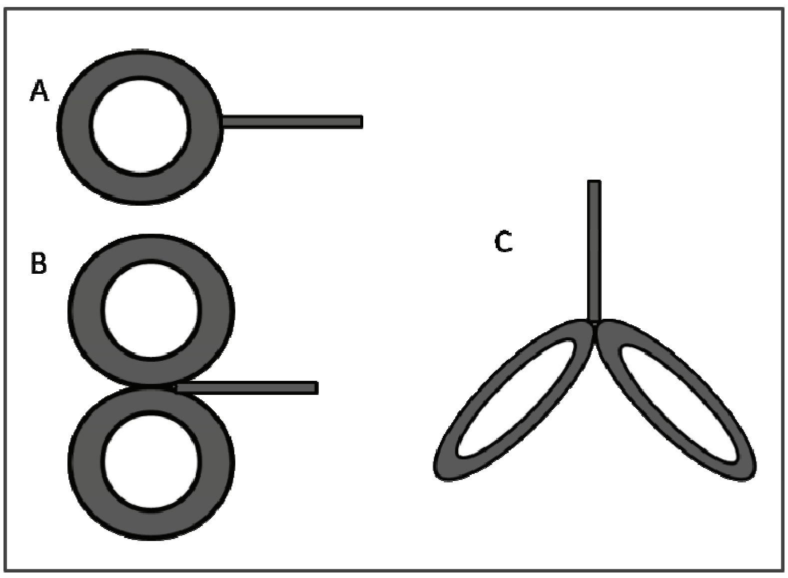

Fig. 5. TMS coil shapes: a) circular coil; b) figure-of-eight coil; c) double- cone coil

The TMS stimulus is also applied in several different protocols: as a single pulse, i.e., it is applied without repetition, generally to define or evaluate a stimulus threshold, or to disrupt a specific cognitive function; as a paired-pulse that is defined as a pair of TMS pulses applied consecutively from a single coil (one sub-threshold habituation pulse followed by a supra-threshold stimulus pulse) it is used to study intra-cortical inhibition and facilitation (Chen, et al. 1998, Kujirai, et al. 1993). For example, when TMS is delivered to motor cortex with an inter-stimulus interval of 1–4 ms, the first pulse suppresses the amplitude of the motor potential evoked by the second pulse, consistent with intracortical inhibition. However, with intervals of 8–15 ms, the second pulse evokes a larger motor potential than an equivalent single-pulse TMS, consistent with intra-cortical facilitation. Another common setup is the double-coil wherein the TMS pulse is applied simultaneously through two coils positioned in two different brain regions; it has been used for studying intra-cortical interactions and for comparing the processing times of different brain regions. Finally, the most powerful protocol for this technique is the repetitive TMS (rTMS) that generates a train of TMS pulses separated by intervals of less than 1 second, i.e., at frequencies that range from > 1 Hz up to 25 Hz in humans. Basically, the effects of rTMS pulses temporally summate, causing a greater change in neural activity than those changes induced by other protocols, and thereby offering a wide range of applications in basic neuroscience and as a clinical tool. For example, rTMS can induce changes in neurotransmitter systems and hormonal axes (Ben-Shachar, et al. 1997, Burt, et al. 2002, Keck, et al. 2000, Keck, et al. 2002, Kole, et al. 1999, Post, et al. 2001). It can also regulate the expression of some genes and the synthesis of some peptides that are important for neuronal plasticity and synaptic development (Keck, et al. 2000, Lisanby, et al. 2000, Schlaepfer, et al. 2004). Depending upon the intensity of the stimulus, rTMS either has anticonvulsant properties in epileptic patients, or reduces the threshold for seizure (Griskova, et al. 2006, Lisanby, et al. 2000, Wassermann, et al. 2001). rTMS is also used as a antidepressant treatment (Daskalakis, et al. 2008), and after significant positive results from numerous clinical trials, it was approved recently by the US Food and Drug Administration (FDA). Nevertheless, since rTMS can induce seizure, it poses some risk to people (Anand, et al. 2002).

Safety

Some safety issues are related to rTMS studies, mainly high-frequency protocols. Single-pulse TMS and low frequency rTMS (<1Hz) in healthy adults appears to carry little risk beyond occasionally causing local discomfort at the site of stimulation or a transient headache in susceptible subjects; no short- or long-term sequela have been described in safety studies with either modality in presumed normal adults (Anand, et al. 2002). Also, there have been no reports of ill effects after magnetic stimulation of the peripheral nervous system and, in the case of cortical stimulation, the incidence of side effects has been extremely low, and well within that expected numbers from statistics for various patient groups (Kandler 1990).

High frequency, high-intensity repetitive TMS (rTMS) carries some risk of inducing seizure even in normal subjects (Anand, et al. 2002, Wassermann 1998). In the ten years since research with TMS started (1985), there were seven documented accidental seizures. For this reason, a group of experts gathered in 1996 to review data on the safety of rTMS and to develop guidelines for its safe use; their findings were published in 1998(Wassermann 1998), detailing all possible rTMS risks and proposing safe guidelines to minimize them . Since then, rTMS risks declined considerably; ten years later a workshop held in Italy again reviewed the safety issues of TMS application; a summary was published in 2009 (Rossi, et al. 2009).

Unwanted long-term effects are also another important safety concern with TMS studies. Even though there are no registered long-term lasting effects for single-pulse TMS (Bridgers 1991, Chokroverty, et al. 1995),(Sack, et al. 2003) , some studies with high-frequency rTMS recorded mild effects persisting for about one hour after the TMS session (Flitman, et al. 1998, Little, et al. 2000, Triggs, et al. 1999), (Sack, et al. 2003). Hence, the first published guideline recommended some precautions with high frequency/intensities rTMS studies, for example, including a of pre- and post-neurological and/or neuropsychological examination, with another follow-up one (Wassermann 1998). Nevertheless there is no evidence of permanent, sustained negative sequelae of rTMS, and long-term cognitive- and neuropsychological-changes after single rTMS sessions are considered negligible in the second guideline based on the preceding bibliography. However, when cumulative daily sessions of rTMS are administered therapeutically, the latest guideline strongly recommended employing neuropsychological monitoring (Rossi, et al. 2009).

Some TMS devices have received FDA approval for peripheral nerve stimulation; cortical stimulation remains investigational. Studies performed with TMS are classified in two groups: a) Non-significant risk (NSR), and, b) significant risk (SR). The former may only require an IRB-approved protocol and consent; SR studies additionally require FDA approval.

General applications

Since 1985, when the first TMS equipment was developed, TMS has been extensively used to explore aspects of human brain physiology in basic neuroscience, and in clinic applications. Initially TMS has shown to alter excitability thresholds and response latencies in several clinical circumstances, such as in people with certain diseases (Berardelli, et al. 1991) and those taking specific medications (Ziemann, et al. 1996). Thus, it was used to measure the cortical excitability thresholds in studies of epilepsy (Werhahn, et al. 2000)], and to improve motor conduction in patients with such deficits, viz., Parkinson's disease (Pascual-Leone, et al. 1994). Its application was also extended to studies of motor function in schizophrenic patients (Puri, et al. 1996), and for the prognosis of recovery from stroke (Rapisarda, et al. 1996). Treating depression was the major application of TMS (George, et al. 1995, George, et al. 1997, Pascual-Leone, et al. 1996); several years of clinical trials clearly demonstrated the value of this technique as an alternative treatment tool for patients who do not tolerate existing medications. Due to its great success, the FDA recently approved TMS for treating depression. TMS improves mood in depressive patients; accordingly, there was an increased interest in using TMS to clarify its effects on mood improvement that now is considered as a consequence of the production of neuroendocrine effect (Keck, et al. 2001). It was also verified recently that TMS can induce the stimulation of striatal dopamine release (Strafella, et al. 2001), the modulation of neurotransmiters (Keck, et al. 2000) and an increase of blood flow in the stimulated regions and connected areas (Speer, et al. 2000).

Researchers in the cognitive and behavioral neurosciences are exploring the ability of TMS to generate artificial lesions temporarily or to turn off the function of specific cortical regions, thereby allowing the functional identification of those brain areas more essential for a given task. Initials neuroscience studies with TMS were limited to animals or humans with pathological lesions; currently, researchers are extending their explorations to the healthy population. For instance, TMS is employed concurrently with some cognitive/behavioral tasks either to disrupt the execution of an specific task by perturbing some fundamental brain regions, or to improve performance by interrupting unimportant and/or competing brain signals (Walsh, et al. 1998). TMS impaired performance during learning and a spatial-memory task (Muri, et al. 1995), and suppressed visual perception during some visual tasks (Amassian, et al. 1989, Beckers, et al. 1995, Miller, et al. 1996), It also was used to investigate the effects of speech on the excitability of the corticospinal pathways of hand muscles (Tokimura, et al. 1996), and the response of transcallosal connections after magnetic stimulation compared with electrical stimulation(Cracco, et al. 1989). The system of callosal fibers activated by transcranial magnetic stimulation revealed the topography of fibers in the human corpus callosum mediating interhemispheric inhibition between the motor cortices (Meyer, et al. 1998). TMS was used to assess the plasticity of the cortical topography in normal volunteers (Pascual-Leone, et al. 1994) and in patients suffering from stroke (Caramia, et al. 1996, Hamdy, et al. 1996) and amputations (Kew, et al. 1994).

4. The Simultaneous TMS & fMRI

The TMS technique rests on the implicit assumption that the induced magnetic stimulation locally disrupts neural activity at the site of stimulation, inducing changes in the correspondent behavioral performance. However, recent TMS-functional magnetic resonance imaging (fMRI) studies imply that the neural consequences of focal TMS are not restricted to the stimulation site (Bestmann, et al. 2003, Bestmann, et al. 2004, Ruff, et al. 2006, Ruff, et al. 2008), but spread throughout different brain regions. Accordingly, the only satisfactory way to directly assess the neural effects of a TMS stimulus is by simultaneously combining TMS and functional brain-imaging techniques(Sack 2006).
This combination opens up a new venue in neuroscience research. TMS supports a focused, controlled manipulation of neural activity, while the imaging techniques allow the functional evaluation of the brain's response to this local neuronal interference. Researchers have explored this multimodality combination of TMS and positron emission tomography (PET)(Paus, et al. 1997, Paus, et al. 1998), single-photon emission computed tomography (SPEC)(Fregni, et al. 2006)], electroencephalography (EEG) (Schutter, et al. 2006, Thut, et al. 2003), near- infrared spectroscopy (NIRS) (Hada, et al. 2006), fMRI (Bastings, et al. 1998, Boroojerdi, et al. 1999, Boroojerdi, et al. 2000, Devlin, et al. 2003, Roberts, et al. 1997), either simultaneously or in separated sections. However, because the simultaneous combination of TMS and fMRI is noninvasive, this is the most promising tool for neuroimaging research, as it allows us to stimulate brain circuits while monitoring changes in the brain's activity and behavior in humans (Bohning, et al. 1999, Caparelli 2007, Hallett 2000, Hallett 2007, Siebner, et al. 2003). This methodology can help to identify brain networks associated with a specific function, supporting causality for brain-behavior connections, and to assess directly the neural effects of a TMS stimulus across the entire brain. However, the direct interaction between the TMS pulse and the MRI scanners poses a considerable technical challenge; thus, few research groups have implemented this approach successfully (Bestmann, et al. 2003, Bohning, et al. 2003)

TMS and fMRI – Technical issues

The main technical issue in simultaneously implementing TMS and fMRI lies, in safely and correctly, positioning the TMS inside the MRI scanner. When two magnetic fields are generated at the same space they interact and induce a reaction force over the sources that will rotate them to align the source's poles, a phenomenon called the torque reaction. For example, when a magnet is in the presence of an external magnetic field, it experiences a torque that tends to align the magnet's poles with the direction of the magnetic field's lines. Similarly, when a TMS coil generates a time- varying magnetic field inside an MRI scanner, i.e., under another high static magnetic field, a torque reaction will act over the TMS coil (Reitz, et al. 1993). These torque reactions are proportion to the scanner's external magnetic field, and depend on the coil's shape and composition (ferromagnetic or non-ferromagnetic), and current direction inside the TMS coil. For example, in a figure-of-eight MRI-compatible TMS coil, using a biphasic stimulator, that generates electrical currents flowing in the opposite direction (Figure 6), the torque reaction is not considered strong (Bohning, et al.

1998); however, it may be significant if another coil shape, or a monophasic stimulator is used. Therefore, to accurately and safely place the TMS coil on the chosen brain site for magnetic stimulation inside the MRI scanners, each MRI center has customized the coil holders to fulfill their needs according with their experiment set up. Thus, Bestmann and colleagues (2003) attached a plastic holder to the head RF-coil that can be manually adjusted (Bestmann, et al. 2003); the wooden approach has been also used as an MRI compatible TMS coil holder (one example developed at BNL, appears in Figure 7 and another in ref. (Bestmann, et al. 2004). A further approach is the semi- automatic TMS coil positioning/holding system, developed by Bohning and colleagues; it is a compact holder, manually operated with 6 calibrated degrees of freedom and with a software package for transforming the MR images' coordinates to the MRI scanner space coordinates (Bohning, et al. 2003).

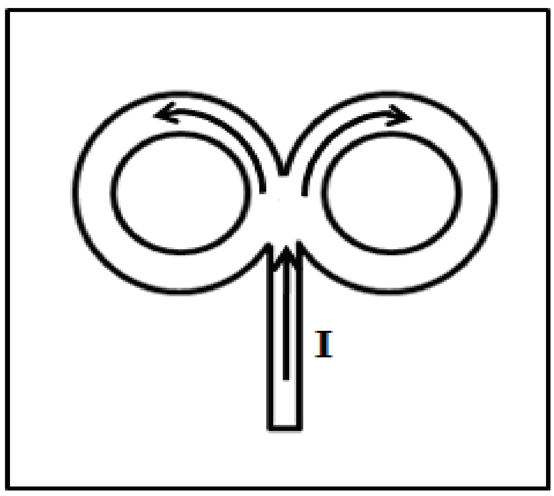

Fig. 6. Figure-of-eight TMS coil with the shown the current directions when used in a biphasic stimulator

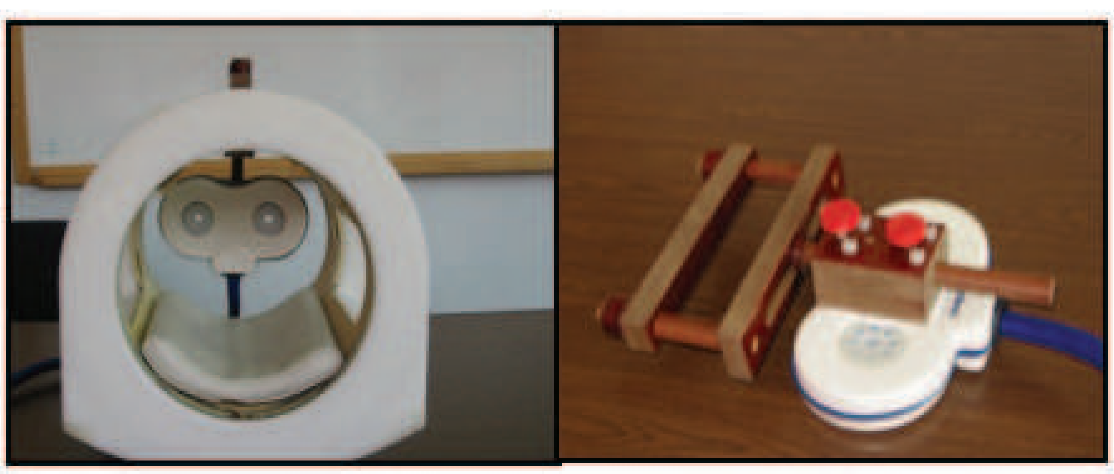

Fig. 7. Picture of the TMS coil holder developed at Brookhaven National Laboratory; left: RF-coil, TMS coil, and coil holder; and, right: TMS coil and coil holder.

The other technical issue associated with this multimodality combination is the interference generated by the TMS coil and the MRI's imaging acquisition process, which was explored by the "pioneers" in using this multimodality technique (Bestmann, et al. 2003). In a magnetic field of 2 Tesla, aliasing and/or susceptibility artifacts might occur, depending on the orientation of the TMS coil and image acquisition, Furthermore, the TMS pulse can interfere with the image acquisition if the interval between the TMS pulse and the first RF excitation pulse is less than about 100 ms. New versions of the MRI-compatible TMS coil minimize the possibility of having aliasing artifacts, while the outcomes of susceptibility artifacts (Figure 8), and the timing between the TMS pulse and image acquisition vary with different magnetic fields.

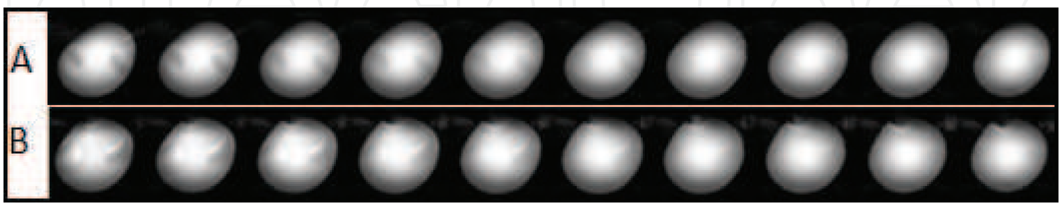

Fig. 8. Round water-phantom coronal images obtained in a 4 Tesla Varian scanner at Brookhaven National Laboratory, without the TMS coil (A), and with the TMS positioned, as shown in figure 7, perpendicular to the image orientation. Local artifacts are observed at the contact point between TMS coil and the phantom (top of fig. B).

Initial applications

The feasibility of simultaneous TMS and fMRI was initially demonstrated in 1.5 Tesla MRI scanners using low frequency TMS protocols (single-pulse TMS or 1 Hz rTMS) and it was considered relatively safe (Bohning, et al. 1998, Bohning, et al. 1999, Bohning, et al. 2000, Bohning, et al. 2000, Bohning, et al. 2003). These researchers used the simultaneous TMS-fMRI technique to evaluate brain activation induced by TMS stimuli of varying intensity applied over the motor cortex region. They directly correlated stimulus intensity and brain activation, but, even though the activated networks generated by different intensities were similar, the areas activated by supra-motor-threshold TMS displayed a bigger BOLD signal than those resulting from sub-motor threshold TMS stimuli. They have also observed some activation in the auditory cortex from the loud noise caused by TMS pulse.

Later studies employed this combination to explore brain activation induced by TMS stimulus given in different brain regions (Nahas, et al. 2001), and with higher rTMS frequencies in higher static magnetic fields, such as 2 Tesla (Baudewig, et al. 2001, Bestmann, et al. 2003) and 3 Tesla MRI scanners (Bestmann, et al. 2004), while also varying the stimulus intensity. These groups verified once more that higher stimulus intensity induces activated areas with a larger cluster size than those activated by a stimulus of lesser intensity. Furthermore, they observed that highfrequency rTMS induces brain activation in a larger network than that induced by a lower rTMs frequency. Thus, in applying a 4 Hz rTMS stimulus at two intensities , supra- and sub-threshold, over the left supplementary motor cortex (M1/S1) in a 2 T MRI scanner, Bestmann and colleagues observed brain activation on the site of stimulation, bilaterally on the right M1/S1, supplementary motor cortex (SMA) and lateral premotor cortex (LPMC) for supra-threshold TMS stimulus. In constrast, there were no significant BOLD-fMRI responses to sub-thresholds stimulations at the stimulus site, but they were evident at distant brain regions, viz, the SMA, LPMC and contralateral M1/S1. (Bestmann, et al. 2003).

Current situation - possibilities and limitations

Existing research results, using the simultaneous combination of TMS and fMRI in different magnetic field intensities, already demonstrated that the technique is feasible and sufficiently safe as a routine research tool in normal volunteers. Its use was extended from the motor cortex to others brain areas, such as the premotor cortex (Bestmann, et al. 2005), frontal-eyes-field (Ruff, et al. 2006), parietal cortex (Ruff, et al. 2008) and occipital area (Caparelli, et al. 2010). The published studies show that this multimodality technique provides the ability to monitor BOLD response while allowing the precise selection of the anatomic- and functional-targets through TMS stimulus, so affording a robust tool for investigating the connection between the TMS action in the cortex areas, and the subsequent BOLD response in subcortical regions.

Nevertheless, although the feasibility of this combined technique is well established, and its several advantages for neuroimaging research enumerated, simultaneous TMS and MRI still technically challenges most research centers. Accordingly, more technical development is needed to reduce the size and shape of the TMS coils so they can fit inside the current multichannel receivers RF-coils. Further, since current MRI compatible TMS coil shape restrict the areas of stimulation to the cortical region, progress is much needed to ensure we can apply a deep TMS stimulus and simultaneously measure the brain's response.

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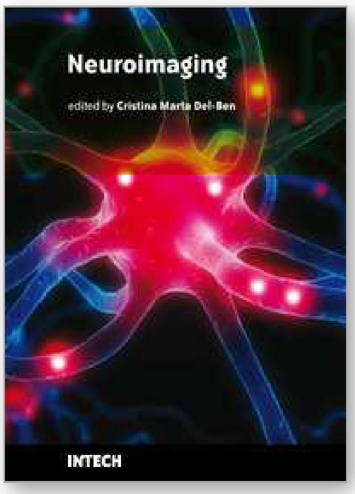

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Neuroimaging has become a crucial technique for Neurosciences. Different structural, functional and neurochemical methods, developed in recent decades, have allowed a systematic investigation on the role of neural substrates involved in functions performed by the central nervous system, whether normal or pathological. This book includes contributions from the general area of the neuroimaging to the understanding of normal functions and abnormalities of the central nervous system.