Brain Stimulation (2009) 2, 58–80

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ORIGINAL RESEARCH

Consensus paper: Combining transcranial stimulation with neuroimaging

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Submitted October 21, 2008. Accepted for publication November 30, 2008.

1935-861X/09/$ -see front matter
doi:10.1016/j.brs.2008.11.002

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In the last decade, combined transcranial magnetic stimulation (TMS)-neuroimaging studies have greatly stimulated research in the field of TMS and neuroimaging. Here, we review how TMS can be combined with various neuroimaging techniques to investigate human brain function. When applied during neuroimaging (online approach), TMS can be used to test how focal cortex stimulation acutely modifies the activity and connectivity in the stimulated neuronal circuits. TMS and neuroimaging can also be separated in time (offline approach). A conditioning session of repetitive TMS (rTMS) may be used to induce rapid reorganization in functional brain networks. The temporospatial patterns of TMS-induced reorganization can be subsequently mapped by using neuroimaging methods. Alternatively, neuroimaging may be performed first to localize brain areas that are involved in a given task. The temporospatial information obtained by neuroimaging can be used to define the optimal site and time point of stimulation in a subsequent experiment in which TMS is used to probe the functional contribution of the stimulated area to a specific task. In this review, we first address some general methodologic issues that need to be taken into account when using TMS in the context of neuroimaging. We then discuss the use of specific brain mapping techniques in conjunction with TMS. We emphasize that the various neuroimaging techniques offer complementary information and have different methodologic strengths and weaknesses.

Keywords transcranial magnetic stimulation; TMS; neuroimaging; multimodal brain mapping; EEG; fMRI; MRI; PET; NIRS; MEG

Transcranial magnetic stimulation (TMS) is an important method for noninvasive stimulation of the human cortex through the intact skull without producing significant discomfort.[1] TMS uses a rapidly changing magnetic field to induce brief electric current pulses in the brain that can trigger action potentials in cortical neurons, especially in superficial parts of the cerebral cortex. In a clinical setting, TMS is mainly used to examine the functional integrity of the corticospinal motor projections.

Since its introduction in 1985,[1] the scientific applications of TMS have rapidly expanded. TMS has become a valuable tool to probe the excitability of intracortical circuits in the motor and visual cortex.[2] TMS produces a synchronized activation of cortical neurons, followed by a long-lasting inhibition. This explains why single pulses or short bursts of TMS can effectively perturb ongoing neuronal processing in the stimulated cortex. This transient disruptive effect of TMS, often referred to as "virtual lesion,"[3] has been extensively used by cognitive neuroscientists to examine the functional relevance of the stimulated area for behavior.[3-5] It should be noted, however, that the disruptive effect of TMS may not always adversely affect task performance. Under certain circumstances, the neurodisruptive effect of TMS may even result in a paradoxical improvement of behavior because of complex interactions at a systems level (eg, interhemispheric or intrahemispheric interactions).[6,7]

Dual-site TMS can induce coordinated stimulation of two interconnected cortical areas. Using a conditioning-test approach, dual-site TMS has been applied to assess cortico-cortical connectivity of pathways projecting onto the primary motor hand area.[8] When long continuous trains or short intermittent bursts are repeatedly applied to a cortical area, repetitive TMS (rTMS) can induce changes in neuronal excitability that persist beyond the time of stimulation.[9,10] These neuromodulatory effects of TMS have been exploited in many in vivo studies on cortical plasticity[11,12] and may be of some use in patients with neurologic and psychiatric diseases to maintain or restore brain function.[13]

Brain mapping benefits from transcranial stimulation

In the last 2 decades, advances in functional mapping techniques have revolutionized human brain research, providing a sensitive means of identifying brain regions where neuronal activity correlates with behavior. Although brain mapping can readily identify the spatial extent and the temporal profile of brain activation during an experimental task, the "correlative nature" of these techniques precludes conclusions about the causal importance of an activated brain area to task performance. In contrast to neuroimaging techniques, TMS is an interventional method that can be used to transiently and reversibly interfere with ongoing neuronal activity in the stimulated neuronal circuitries of the brain.[14] The "interventional nature" of TMS has added a new dimension to human brain mapping, opening up unique possibilities to probe causality at the systems level of sensory, cognitive, and motor brain networks.[8] For instance, when TMS is applied during an experimental task, its perturbative effects can be used to make causal inferences regarding the functional contribution of the stimulated cortex to a specific brain function.[4] In addition, the high temporal resolution of single-pulse TMS can be exploited to identify critical periods during which the stimulated area and its connections to other brain regions make a critical contribution to the experimental task (often referred to as chronometry).[3] Hence, the combined TMS-neuroimaging approach is capable of tracing the temporospatial dynamics of causal interactions within functional brain networks.

TMS can also be used to activate and study mechanisms of acute cortical reorganization in the healthy human brain. This is achieved by applying periods of rTMS over a target area to produce effects on cortical circuits that outlast the duration of the rTMS session. The functional after effects that can be elicited with rTMS depend on the variables of stimulation such as intensity, frequency, and total number of stimuli and the functional state of the cortex targeted by rTMS. These neuromodulatory effects have great potential for studies on adaptive neuroplasticity in the human brain.[12] Critically, the conditioning effects of rTMS are not limited to the stimulated cortex, but focal rTMS gives rise to functional changes in interconnected cortical areas as well.[12] Functional brain mapping techniques offer a wide range of methods to map the temporospatial patterns of local and distal reorganizational changes in brain function. As such, neuroimaging offers a valuable means of exploring how rTMS impacts on the human brain, providing new insights into the changeability of functional brain networks.[15-17]

Transcranial stimulation benefits from brain mapping

It is worth bearing in mind that TMS represents a nonphysiologic means of producing neuronal activity in the human brain. A key question is how this nonphysiologic mode of brain stimulation interacts with the intrinsic neuronal activity in the human brain. Motor evoked potentials (MEPs) or TMS-induced percepts (eg, phosphenes) have been used to explore how TMS excites the human cortex. Most of the knowledge about the physiologic mechanisms of actions has been gathered with TMS of the primary motor hand area (M1-HAND) in studies that recorded MEPs elicited by single or paired transcranial stimuli in a contralateral hand muscle. Other studies examined the behavioral consequences of TMS in well-defined experimental tasks. Although these studies can highlight the functional involvement of cortical areas in perception, cognition, and motor control, they provide no clues regarding the physiologic mechanisms that cause or prevent a TMS-evoked change in behavior. The limited insights into the mechanisms of action revealed by MEP recordings or behavioral testing motivated the use of neuroimaging techniques to map the acute and conditioning effects of TMS on brain function.

General considerations

The timing of TMS relative to neuroimaging

The timing of TMS in relation to neuroimaging defines which questions can be tackled using a combined TMS-neuroimaging approach (Figure 1). In principle, TMS can be applied while neuroimaging is being performed (referred to as "online" TMS-neuroimaging approach). Online neuroimaging experiments are technically demanding because TMS may adversely affect data acquisition during neuroimaging. This requires methodologic refinements to effectively avoid or control for TMS induced artifacts, especially when combining TMS with electroencephalography (EEG) or functional magnetic resonance imaging (fMRI).

Alternatively, TMS may be applied "offline" before or after neuroimaging. This "offline" TMS-neuroimaging approach is technically easier to establish because rTMS and neuroimaging are separated in time. TMS and

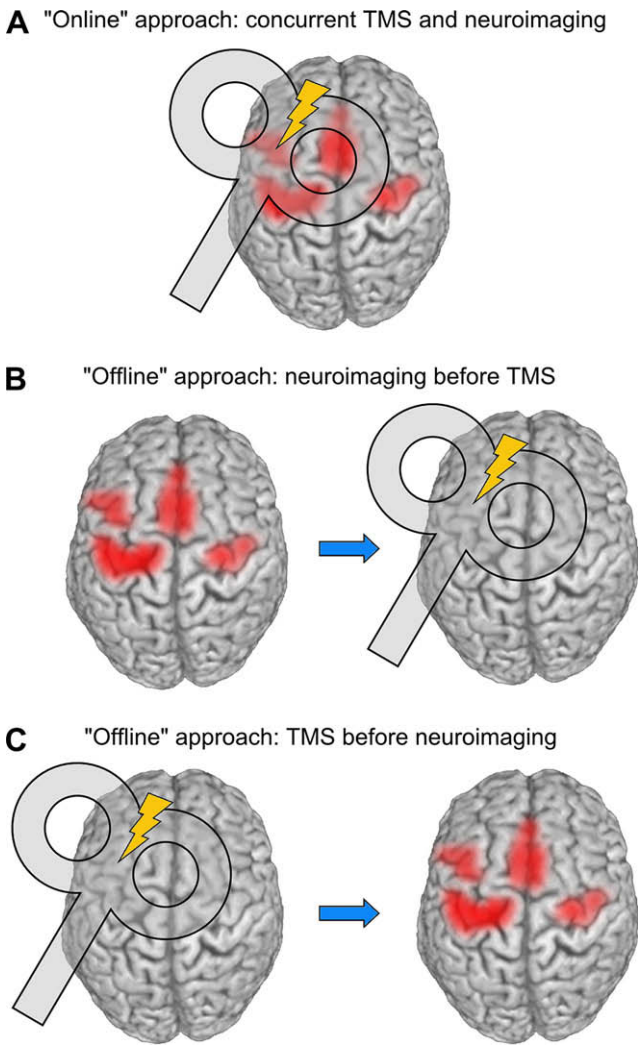

Figure 1 The "online" TMS-neuroimaging approach applies TMS while brain mapping is being performed **(A).** The "offline" TMS-neuroimaging approach separates TMS from neuroimaging in (space and) time: neuroimaging may be performed before TMS is applied **(B)** or neuroimaging is performed after the brain has been conditioned with TMS **(C).** TMS = transcranial magnetic stimulation.

neuroimaging can also be separated in space. For instance, TMS can be applied outside the MRI suite when conducting an offline rTMS-fMRI study. In practice, no specific methodologic precautions are necessary when offline TMS is combined with any of the available neuroimaging techniques. (Refer to Table 1 for terminology and definition of the various TMS-neuroimaging approaches to which we refer in this consensus paper.)

Online approach: Neuroimaging during TMS

TMS may be performed during neuroimaging (ie, online TMS). In this case, neuroimaging provides a temporospatial assay of the immediate effects of TMS on neuronal activity ("perturb-and-measure" approach; Table 1). If the experiment systematically varies the functional state of the brain at the time of stimulation, concurrent TMS-neuroimaging can probe how the "neuronal context" at the time of stimulation determines the induced activity changes locally as well as in connected brain areas (also shown by transcranial electric stimulation[18,19]).

The interpretation of online neuroimaging studies is complicated by the fact that TMS results in multimodal sensory stimulation. In addition to the "direct" cortical effects induced by the time-varying magnetic field, TMS has multiple "indirect" effects on brain activity.[20] TMS elicits auditory and somatosensory sensations (eg, activation of the cochlea, trigeminal activation). The TMS-associated sensory stimulation may produce a startle response or be perceived as unpleasant. All of these effects largely depend on the site and intensity of the stimulation being delivered. These indirect effects related to the multisensory nature of TMS need to be considered and controlled for. Furthermore, experiments and subsequent analysis must be carefully designed and executed, taking into account these potential confounds.[20] This includes

Table 1 Terminology and definition of TMS-neuroimaging approaches

Online TMS-neuroimaging	Concurrent application of TMS and neuroimaging
"perturb-and-measure"	Neuroimaging during application of single-pulse or burst-rTMS to measure the immediate and transient neuronal responses caused by TMS perturbation.*
Offline TMS-neuroimaging	Consecutive application of TMS and neuroimaging
"map-and-perturb"	Neuroimaging before TMS to map the brain regions/networks involved in a given task to identify target sites for subsequent (1) conditioning with rTMS to alter* neuronal processing in a subsequent behavioural task or (2) single-pulse or burst-rTMS applied during a behavioural task to transiently perturb* neuronal processing (so-called "virtual lesion") within specific time windows
"condition-and-map"	Neuroimaging after conditioning with rTMS to map brain areas/networks that show persistently altered* activity during subsequent (1) resting-state (eg, due to metabolic changes) or (2) task performance (eg, due to rapid reorganisation)

TMS = transcranial magnetic stimulation; rTMS = repetitive TMS.
*Principally, despite the acute perturbation of neuronal processing, rTMS as well as single-pulse or burst-rTMS can both inhibit and facilitate task performance on a behavioral level, critically depending on target area, timing of stimulation and the nature of the task.

possible interactions among brain areas activated by the direct effects of TMS on brain activity and indirect (cross-modal) effects on brain activity associated with the multisensory nature of TMS.

Offline approach: Neuroimaging before TMS

Neuroimaging may be performed before a TMS experiment to reveal the temporal (eg, with EEG) or spatial (eg, with fMRI) brain activation pattern during the performance of an experimental task. The temporospatial information of regional task-related activity can then be used to define the optimal time window during which TMS should be applied during a task and to guide the placement of the coil over the cortical target side. This a priori knowledge is of particular value when designing experiments in which TMS is used to interfere with task performance.

This "map-and-perturb" approach (Table 1) can be used to make causal interferences about the contribution of a cortical area or its interconnected network to a distinct brain function. Although functional brain mapping techniques can reliably identify networks that are activated during an experimental task, the correlational nature of neuroimaging precludes any inference about the causal importance of a regional brain activation for behavior. This question can be addressed using TMS. TMS can be applied over the area of interest to disrupt regular neuronal processing while participants perform the same experimental task. If TMS modulates task performance, it can be concluded that the stimulated cortical area or its closely interconnected areas make a relevant contribution to the task.

An early demonstration of this approach was given by Cohen et al[21] in a TMS study on blind subjects. Previous neuroimaging studies had shown that Braille reading consistently activated visual cortical areas in blind subjects but not in those with sight. To investigate the significance of task-related activation in the occipital cortex, short trains of 10-Hz rTMS were applied over several brain regions time-locked to Braille reading. Occipital rTMS induced errors and distorted the tactile perceptions of congenitally blind subjects but had no effects on tactile performance in the normal sighted. This finding proved that the occipital visual cortex makes a relevant contribution to the processing of tactile input in blind subjects.

In addition, neuroimaging is of great value to localize functionally the optimal site for TMS in individual subjects. One possibility is to let subjects perform the experimental task during fMRI and use the regional peak activation to define the target for subsequent TMS.[22] Individual peak activations can then be superimposed on the structural image of the subject's brain and inform frameless stereotaxy where to position the coil over the cortical region that is to be targeted with TMS. An alternative strategy is to base the coil placement on the group result revealed by a functional neuroimaging study that had used the same or a similar experimental task. The stereotactic coordinates of task-related peak activation in the area of interest defines the site of stimulation. This voxel is marked in the normalized structural MRI of each subject who participates in the TMS experiment. The individual site of stimulation can then be derived from the normalized MRIs by reversing the normalization procedure.

Offline approach: Neuroimaging after TMS

Neuroimaging techniques have a great potential to map temporospatial patterns of functional reorganization that are induced in the human brain by rTMS.[12] This scenario requires that neuroimaging needs to be performed after a conditioning session of rTMS. This "condition-and-map" approach (Table 1) probes the changeability of functional brain networks. Among other possibilities, neuroimaging after rTMS conditioning can map the lasting functional impact of rTMS on task-related neuronal activity at a systems level.[16,17] Neuroimaging should start as quickly as possible after rTMS to ensure that short-lasting after-effects of rTMS are captured. The task specificity of functional reorganization can be shown by having participants perform an additional control task during the same fMRI session.

One way of detecting the conditioning effects of rTMS on regional neuronal activity is to compare task-related activation before and after rTMS. However, any change in activation may simply be a time effect caused by the fact that the experimental task has been repeatedly performed in the MRI scanner. To dissociate temporal order effects from "real" effects that are causally related to rTMS, the experimental design should include a control session in which subjects perform the same experimental task but without effective rTMS. The order of the "real rTMS" session and control session should be counterbalanced across subjects, or within the same subjects on different days. In the control session, sham rTMS might be applied to the cortical target area. Ideally, sham rTMS should be matched to real rTMS in terms of auditory and somatosensory stimulation but without effective transcranial stimulation of the cortex. A specific change in the pattern of task-related activation after real but not after sham rTMS would indicate a true reorganisation in response to rTMS conditioning.

Temporal and spatial resolution

The temporal and spatial resolution of neuroimaging techniques represents important selection criteria when planning a combined TMS-neuroimaging study (Figure 2). If temporal aspects of neuronal processing are the main focus, the use of a neuroimaging method with a high temporal resolution such as EEG will be preferable. Conversely, a neuroimaging method with good spatial resolution and whole brain coverage such as fMRI will be appropriate if the goal of the experiment is to test the spatial pattern of TMS-induced changes in brain activity.

It is also worthwhile to consider the temporal and spatial resolution of TMS in the context of neuroimaging. The spatial resolution and penetration depth of TMS are limited. When using a figure-8 shaped coil, the maximum electric field induced in the brain lies in the junction region with the area of effective stimulation being several square centimeters. The volume of tissue stimulated by any TMS coil depends on many factors, including the geometry of the coil, stimulus configuration, stimulus intensity, and the electrical properties of the stimulated cortex. Another important feature of TMS is that the induced electric field decreases very rapidly with distance from the TMS coil. Hence, TMS induces stronger electric currents in superficial regions than in deeper structures. This explains why superficial cortical areas are relatively easy to stimulate, whereas those cortical areas that are located far from the scalp surface are much harder to stimulate. The attenuation of the induced electric field with the distance from the coil also explains why deep brain structures such as the thalamus and basal ganglia cannot be directly stimulated with conventional TMS coils. However, it is important to emphasize that TMS can effectively activate neuronal outputs that project from the stimulated site to other distant areas of the brain. This means that TMS can modify

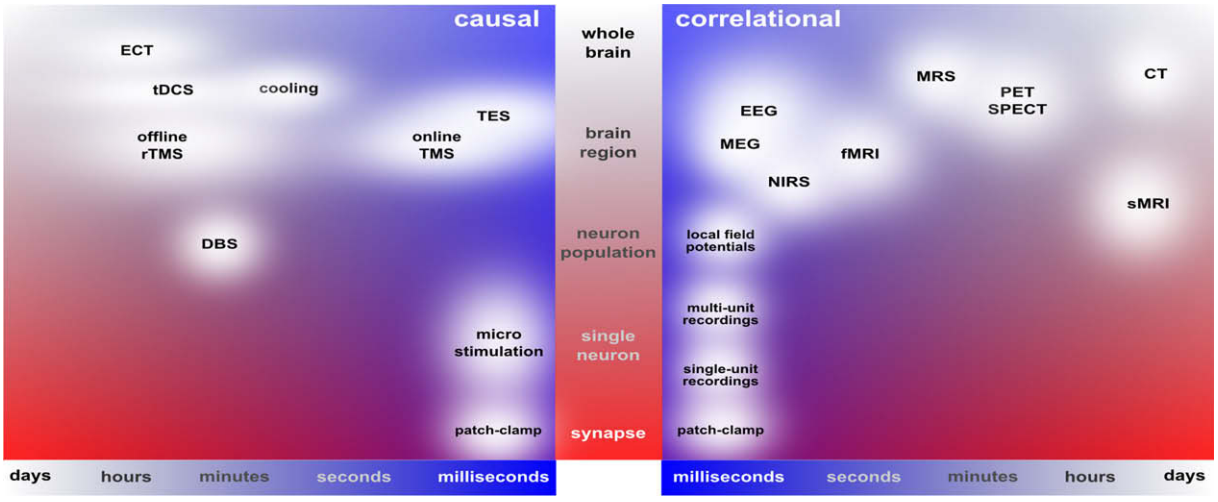

Figure 2 Different temporal and spatial scales: Neurostimulation and neuroimaging techniques are arranged according to their temporal and spatial resolution.

ongoing neuronal activity within complex neuronal circuits, and not just those at the site of stimulation.

The temporal resolution of TMS depends on how TMS is applied (Figure 2). A single TMS stimulus will induce an electric current in the brain lasting less than 1 millisecond. The electric current in the brain tissue causes a synchronized high frequency burst of discharge in a relatively large population of neurones that is terminated by a long-lasting GABA-ergic inhibition. This TMS-induced change in neuronal activity can last for several hundred milliseconds depending on the intensity of TMS. If short bursts of high-frequency ($\geq$ 5 Hz) TMS are applied, the influence of TMS on neuronal activity can be prolonged, lowering the temporal resolution of TMS. Finally, TMS protocols that apply prolonged trains of TMS can induce changes in neuronal excitability that may last for more than 1 hour after the end of TMS.[9,12] These persisting offline effects on brain activity that can be observed after rTMS conditioning are likely to differ substantially from the acute neuronal excitation that is directly induced by the time-varying magnetic field. The bottom line is that the spatial and temporal resolution of both the neuroimaging method and the TMS protocol, have a substantial impact on the scientific questions that can be tackled with the combined TMS-neuroimaging approach.

Electroencephalography and magnetoencephalography

Basic methodology

EEG is the most commonly used noninvasive recording technique of electric brain activity in humans. By using surface electrodes, the EEG measures voltage changes on the scalp that reflect ion flow caused by excitatory and inhibitory postsynaptic potentials. The scalp EEG is most sensitive to postsynaptic currents of neuronal populations whose dendrites are oriented radially to the scalp (located in the gyri), whereas currents tangential to the scalp (located in the sulci) do produce weaker EEG signals.

Nonradial (tangential or tilted) electric currents, however, are the main source for the magnetic fields that are picked up by magnetoencephalography (MEG), rendering MEG and EEG complementary techniques with otherwise similar temporal characteristics. By using multiple small detector coils, the MEG principally measures the magnetic fields produced by the synchronous postsynaptic currents of neuronal populations. The excellent temporal resolution of both methods lies on the millisecond scale. Spatial resolution, however, essentially depends on the number of recording sites. Although high-density EEG (hd-EEG) or MEG can achieve spatial accuracy close to a few millimeters, the spatial resolution of standard EEG recordings is in the range of several centimeters depending on the number of electrodes. As the small signals (microvolt and femtotesla for EEG and MEG, respectively) rapidly decay over distance, activity in deep brain structures may be difficult to locate with either method. In the case of EEG, there is additional spatial smoothing caused by the tissue compartments between the electrodes and the cortex (skin, muscles, skull, meninges).

EEG can be recorded using a variety of different electrode configurations, ranging from a few electrodes (readiness potentials, somatosensory-evoked potentials) to hd-EEG using 64 or up to 256 channels, depending on the purpose of the study. EEG recordings can reveal temporal and spatial information about externally triggered event-related (event-related potentials, ERPs) or spontaneous brain activity. The measurement of ERPs requires averaging of many short EEG sweeps that are time locked to an experimentally defined event to subtract "neural noise" from the evoked cortical response. Event-related cortical activity can be quantified by measuring latencies and amplitudes of distinct ERP components. Spontaneous EEG is usually recorded over long periods to assess states of vigilance or consciousness like wakefulness and sleep. It can demonstrate transient spontaneous activity like epileptic seizures or sleep spindles. EEG analysis of oscillatory activity is often restricted to distinct frequency bands that are linked to specific neuronal processes.

Technical and safety aspects

When the application of TMS and EEG/MEG acquisition are separated in time (offline approach), the combination of TMS and EEG/MEG is methodologically relatively unproblematic. In offline TMS-MEG studies, TMS should be given outside the MEG room. For combined TMS-EEG studies, the only point to consider is whether TMS should be applied with electrodes being attached to the scalp. The decision might depend on the experimental design as well as number and montage of electrodes. Standard electrodes increase the distance between the TMS coil and the cortex. Therefore, TMS with electrodes in place will require a higher intensity of stimulation to induce a stimulation effect that matches the effect induced by TMS without electrodes. However, extremely flat electrodes have become available to minimize this problem.

The simultaneous use of TMS and EEG/MEG is more problematic relative to the offline approach. Simultaneous use of TMS and MEG is impossible with present techniques because of the huge (15 orders of magnitude) difference between the magnetic field strengths relevant in MEG and TMS. MEG measures the weak time-varying magnetic fields generated by nonradial electric currents in the brain, whereas TMS induces a very strong time-varying electric field to produce a suprathreshold electric current in the cortex. In contrast, online TMS-EEG was first performed in 1997.[23] The main problem that one has to face when applying TMS during EEG is the powerful electric field that is induced by the discharge of the TMS coils in the electrode leads. Considering a typical pulse intensity of 1

Tesla and a rise time of 0.1 millisecond, the voltage induced in the electrodes underlying the stimulator can reach an amplitude of 10 volts. This voltage, being several orders of magnitude larger than the signal produced by the brain, can cause large artifacts in the recordings and may put an ordinary EEG amplifier out of the operating range for a few seconds. In fact, high-quality EEG recording during TMS can only be obtained with specifically designed amplifiers. Up to now, a few different technical solutions have been implemented. Virtanen et al[24] developed a 60-channel TMS-compatible EEG system that includes gain-control and sample-and-hold circuits to block the artifact induced by TMS in the leads. This system pins the acquired signal to a constant level for a couple of milliseconds around the pulse and records TMS-evoked EEG potentials (TEPs) that are completely free from artifacts. An alternative way to deal with the TMS artifact has been implemented by Thut et al.[25] They use a slew-limited amplifier that prevents the electronics from saturating during the TMS pulse resulting in a short-lasting artifact that decays within 30 milliseconds. Finally, Bonato et al[26] have recently used an MRI-compatible DC amplifier with a wide dynamic range to successfully record TEPs preceded by a short artifact (10-20 milliseconds). With this method, recordings have to be obtained without any filtering, as these might interact with the TMS artifact, producing ripples for up to a second. However, filtering can be applied after removing artifacts from the data.[27]

Beside the artifact induced by discharging the transducing coil, additional high-amplitude artifacts lasting several tens of milliseconds are caused by recharging the capacitors of the stimulating device immediately after the stimulation. A possible workaround is to introduce a delay between discharge and the onset of recharging.

Even with an optimal amplifier, TEPs of sufficient quality can only be recorded at the stimulated site if additional measures are taken. During the application of the TMS pulse, some current can pass through the electrode-electrolyte interface, thereby causing a polarization and, possibly, an EEG baseline shift that can last for hundreds of milliseconds.[24] In addition, especially when large traditional electrodes are used, the induced currents can interact with the magnetic field, causing a force and thus movement of the electrodes. Finally, overheating of the EEG electrodes may occur, particularly when long trains of pulses are delivered.[28] All these problems can be effectively addressed using special electrodes, such as ring electrodes with a slit,[2] small Ag/AgCl pellet electrodes, or plastic sensors covered by silver epoxy.[29] In addition, these problems of drift, motion, and heating are only evident at electrode sites immediately underneath the stimulating coil.[24] In all cases, it is strongly recommended to work carefully on the electrode-to-scalp contact to minimize impedances as much as possible. Gently scraping the skin with an abrasive paste before applying the conductive gel normally results in a suitable impedance level (< 5 kOhm). Recently, minipuncturing of the epithelium under the electrode contacts has been suggested to reduce skin resistance and thereby TMS artifact size even further.[30] Electrode leads should be kept relatively fixed and free of loops. Avoidance of physical contact between TMS coil and electrodes (eg, by foam) can reduce some mechanical artifacts induced by coil vibrations.[27] However, this will increase the coil-to-cortex distance and thus, adversely affect the efficacy of TMS.[27]

If the TMS coil is positioned over scalp and facial nerves or muscles, these may be activated, resulting in a large biologic muscle artifact lasting for tens of milliseconds. Unless new strategies, such as optimal pulse shapes or shielding devices, are developed to minimize scalp muscle activation, this kind of artifact can not be eliminated. For now, the problem can be avoided only by moving the coil to a more favorable location (more central scalp regions), or orientation, and/or by reducing the strength of stimulation. The coil's discharge is associated with a loud click (up to 130 dB), which might trigger a blink reflex and thereby eye movement artifacts in the EEG. More importantly, this noise obviously evokes an undesired auditory response that overlaps with TEPs.[31] This major confound can be effectively eliminated by using earplugs and additionally masking the coil's click with white noise, or with a sound that has an optimal spectral content.[32] By stimulating sensory nerve fibers of the cranial nerves, TMS may also trigger somatosensory evoked potentials. However, their contribution to the overall activation appears to be negligible.[26,33] As for behavioral TMS studies, the stimulation of control sites or the use of a proper sham stimulation can be helpful to disentangle the contribution of the different sources.[27]

Although coil placement by means of MRI-guided frameless stereotactical neuronavigation has already become state of the art, it is of superior importance in combined TMS-EEG studies. Small shifts in coil orientation can cause marked changes in TEPs. Here neuronavigation is able to provide a high degree of reproducibility, even across separate sessions.[34] Some commercially available navigation systems even provide an estimation of location and strength of the maximum electric field induced in the cortex based on realistic head models.[35] Future navigation system might also incorporate information about the orientation of axons in the stimulated area.[36]

Neuroscientific and clinical applications

As pointed out above, the simultaneous use (online) is only possible when TMS is combined with EEG (but not with MEG), whereas TMS-MEG as well as TMS-EEG both can be combined consecutively (offline). Furthermore, the majority of published articles in the field have combined TMS with EEG rather than with MEG. Therefore, we will mainly focus on the combination of TMS and EEG in this review.

The offline TMS-EEG approach can be applied in both directions. When using EEG (or MEG) before TMS, the spatial distribution of cortical activity (eg, ERPs) in multichannel EEG can inform the experimenter where to place the TMS coil. More importantly, the excellent temporal resolution of EEG (and MEG) offers the possibility to optimize the timing of TMS based on the temporal signature of task-related EEG activity of each subject. This may help to determine the optimal time window for the induction of disruptive TMS effects in a subsequent behavioral TMS experiment.

Likewise, recordings of ERPs or spontaneous EEG can be used to study the lasting impact of rTMS on cortical processing. For instance, multichannel EEG recordings during sleep demonstrated changes in sleep associated oscillatory activity patterns (ie, slow oscillations and sleep spindles) in response to 5Hz rTMS of the dorsal premotor cortex[37] or paired associative stimulation of the M1-HAND.[38-40] Moreover, using a correlative approach, altered EEG theta power after 40 hours of prolonged wakefulness could be related to changed motor cortical excitability as determined by paired-pulse TMS measurements.[41]

The online TMS-EEG approach offers several additional possibilities. First, the EEG activity just before a TMS stimulus is applied contains information about the functional state of the stimulated cortex at the time of TMS. This information may be used to study the state dependency of the brain's responsiveness to TMS. The regional expression of spontaneous oscillatory activity directly preceding a TMS pulse may be predictive of the brain response to TMS. This has been shown for the expression of occipital alpha activity and the capability to evoke phosphenes with occipital TMS.[42] Second, online EEG recordings have revealed TMS induced changes in the frequency domain. For instance, a single TMS pulse can transiently synchronize activity in the beta range.[43] Furthermore, trains of 1-Hz and 5-Hz rTMS are associated with concurrent changes in cortical alpha and beta activity.[44,45] Third, functional connectivity between cortical areas in a given task can be investigated by probing the effect of TMS over one cortical site on the ERPs evoked in another area. This approach has been used to study the role of the frontal eye fields in controlling visual processing in posterior visual brain areas during the orienting of spatial attention[46] and the influence of the dorsal medial frontal cortex on lateralized action potentials in primary motor cortices during conflict resolution in an action selection task.[47] Application of TMS to the posterior parietal cortex during a visual search task also modulated the occipital N2pc component that is evoked by target detection.[48]

Finally, recording the TEPs provide a means of directly studying the excitability and response characteristics of practically any cortical area that is accessible to TMS. Beforehand, this was possible only by using indirect measures such as MEPs in the primary motor cortex or phosphenes in visual areas. A single TMS-pulse evokes a cortical potential waveform in the EEG, which strongly differs in polarity and amplitude of its peak components depending on several factors such as position and orientation of the TMS coil, stimulation intensity, electrode position, and reference. However, suprathreshold stimulation (biphasic pulse configuration) of the motor hand area with a coil orientation eliciting a posterolateral-to-anteriomedial current in the brain reliably evokes a response at the vertex (referenced to linked mastoids) with the following components: N10, P14, N15/18, P30*, N40/45*, P55/60, N100*, P180/190, and N280 (* indicates the most reliable ones).[26,43,49] As an alternative to peak analysis, especially for hd-EEG recordings, the calculation of *global mean field power* (GMFP)[50] has been introduced as a reference-free measure of local EEG variability. As the number of neurons recruited by a single TMS-pulse is directly related to their excitability, GMFP amplitude change has been proposed as a measure of cortical excitability, which is sensitive to TMS-induced changes in cortical plasticity.[37,38,51] Moreover, in combination with source localization, the temporospatial propagation of TMS-evoked cortical activity can be traced[32,52,53] to gain insight into the temporospatial dynamics of the corticocortical connectivity patterns that are activated by TMS. The online TMS-EEG approach can directly probe regional cortical excitability and corticocortical connectivity in humans. During a typical TMS-EEG session it is possible to (1) measure the strength of its immediate response in the cortical target area of interest,[54] (2) detect the temporospatial dynamics of the ensuing spread of activation,[23,32] (3) calculate corticocortical conduction times,[33] and (4) quantify complex dynamics such as phase locking or power modulation of EEG rhythms.[43-45,55]

Excitability and connectivity are essential properties of the nervous system and are abnormal in many neurologic and psychiatric disorders. They also can be altered by agents affecting brain function such as alcohol.[56,57] As TMS-EEG stimulates and records from the cerebral cortex, by-passing sensory pathways, subcortical structures, and motor pathways, the measurement does not depend on the integrity and status of sensory and motor systems and can be applied to any subject (deafferentiated, paralyzed, unconscious). Future clinical applications of TMS-EEG may therefore include: (1) measuring the excitability and the connectivity of frontal circuits in schizophrenia[58] and depressed patients, (2) measuring corticocortical conduction times in multiple sclerosis and neurodegenerative disorders, (3) monitoring the excitability of the lesioned and the contralateral homologous cortex after stroke, and (4) assessing the state of thalamocortical circuits in patients with impaired consciousness that are unable to communicate. More generally, TMS-EEG can be used to prospectively track and monitor the excitability and connectivity changes occurring in any cortical region during rehabilitation, pharmacologic therapy, TMS treatment, or spontaneous recovery.

Conclusion/Summary

The main advantage of EEG, compared with other TMS-imaging approaches, is its millisecond-scale temporal resolution, which allows one to measure the immediate cortical response to TMS. TMS triggers a combination of fast excitatory and inhibitory events in the stimulated area[59] that may cancel each other if averaged over time. Indeed, although TEPs invariably detect a strong activation in the stimulated area, positron emission tomography (PET) and fMRI often fail to do so.[60,61] In addition, TMS-EEG conveys precise information about the temporal order of activations of distant cortical areas. Likewise, the technique can also reveal, in real-time, TMS-induced oscillations with obvious safety implications and possible practical applications.[52] Its high-temporal resolution renders the EEG method a perfect complement to the transient perturbations caused by TMS in the brain's oscillatory processing modes.

Other advantages of TEPs are their high signal-to-noise ratio and the fact that they can be easily collected at the patient bedside at a relatively low cost. The main disadvantage of TEPs is their low spatial resolution, which can partly be compensated for by increasing electrode density and by performing advanced source modeling, yet the combined TMS-EEG approach is of limited use to map TMS induced activations in deep brain structures. Another limit is its susceptibility to artifacts, such as muscle interference and eye blinks, currently preventing the collection of clean TEPs when temporal and orbitofrontal cortices are stimulated.

The combined TMS-EEG technique is still in its early age and much methodologic work is needed to fully unfold its potential. For example, the contribution of different artificial and noncortical biologic sources to the TEP has yet to be disentangled to allow a fully comprehensive interpretation. Especially the very immediate cortical response to TMS within the first 10 or 20 milliseconds after TMS is still not fully accessible. Further research has to characterize the reproducibility of TEPs and gain normative data as well as knowledge about their changes in health and disease.

Functional MRI

Basic methodology

Among the neuroimaging techniques, the elegance of fMRI lies in its ability to measure the metabolic consequences of neural activity through changes in endogenous oxy- and deoxyhemoglobin concentration. Deoxyhemoglobin is paramagnetic and causes local magnetic field inhomogeneities that reduce the measured MR signal. Consequently, increased deoxyhemoglobin leads to a decreased MRI signal intensity and therefore acts as an endogenous contrast agent. Because this so-called blood-oxygenation-level-dependent (BOLD) contrast is tightly coupled to cerebral blood flow, neuronal activity, and energy use, regional changes in brain activity can be inferred throughout the human brain, including subcortical structures (for a comprehensive overview, ref. [62]). Functional MRI can measure such activity changes with a spatial resolution of a few millimeters. Its temporal resolution is on the order of seconds because changes in blood flow are delayed and more prolonged with respect to the underlying neural responses. Yet the hemodynamic lag is highly constant. Therefore, by using the appropriate design, one can "decorrelate" events and differentiate neural population activity-changes to events only a few hundred milliseconds apart.[63,64] Standard fMRI experiments acquire a large series of brain volumes (images) while the subject performs a task. The ensuing MR signal time series in each volume element (voxel) is then correlated with the experimental manipulation. Consequently, over the past 2 decades, fMRI has been uniquely successful in investigating the functional neuroanatomy in health and disease.

Technical and safety aspects

The high magnetic field strength of modern MRI scanners (between 1.5-7 T) imposes several limitations and challenges for its simultaneous combination with TMS, which was first performed by Bohning et al.[60,65] One can distinguish two principle problems for combined TMS-fMRI: static and dynamic artifacts. The former arise through the mere presence of the TMS setup itself, whereas the latter are due to operating the TMS setup, such as applying TMS pulses during fMRI.

Static artifacts

For safety reasons, all ferromagnetic material must be removed from any equipment (eg, TMS coils) entering the MRI scanner.[60,66] At the same time, MRI-compatible TMS coils need to withstand the increased mechanical stress during MRI. However, the presence of the MRI-compatible TMS coil may still lead to geometric image distortions.[67,68] These can be reduced by a shorter read-out time of echo-planar imaging (EPI) sequences, using stronger imaging gradients and/or parallel imaging. Oversampling of EPI images in phase-encoding direction can shift so-called "ghosting" artifacts outside the central field of view without compromising image resolution and compromising temporal resolution only minimally. Other parts of the stimulator unit must be safely placed outside the scanner room or in a radiofrequency-shielded cabinet inside the scanner room, at sufficient distance from the magnetic fringe field of the MRI scanner. This requires an increase in TMS coil cable length that may bring about unwanted increases in serial inductance, diminished effective TMS coil output,

and increased power requirements. TMS coil movement can be minimized with MR-compatible TMS coil holders that allow safe and accurate placement of the coil inside the scanner. MR-compatible automatic and computer-operated TMS-coil holder and positioning systems provide additional accuracy and reproducible positioning,[69] but are technically more challenging to implement.

Dynamic artifacts

Radiofrequency (RF) noise can additionally affect the signal-to-noise ratio of MRIs, but this may vary widely between different TMS and scanner setups. TMS stimulators may directly generate RF noise (eg, around 64 MHz at 1.5 T), and the antenna-like properties of the TMS coil cable can additionally guide RF noise into the scanner. Customized RF filtering can suppress this noise. Additional image distortions and artifactual signal changes may occur through leakage currents that originate through the high-voltage capacitors of the TMS stimulator. These leakage currents can change with different charge levels (output level) of the TMS machine, and can potentially lead to signal changes that are in the same order as physiologic BOLD signal changes. Remote-controlled high-voltage relay-diode systems can reduce leakage currents flowing between the stimulator and the TMS coil by several orders of magnitude, thus permitting BOLD-sensitive imaging in the direct vicinity of the coil.[70,71] The strong magnetic pulses induced by TMS can furthermore distort MRIs. The size of such distortions depends on several factors, such as TMS coil orientation, TMS pulse intensity, and MRI magnetic field strength.[66,68] The problem can be alleviated by applying sufficient temporal gaps between TMS pulses and subsequent MRI acquisition.[72] Increasing distance between the imaged brain slice and the TMS coil[67,68] further alleviates the problem. Direct TMS pulse–EPI excitation pulse interference should be avoided, and images being perturbed by TMS pulses must be replaced. This can be achieved through interpolation between preceding and subsequent (unperturbed) MRIs.[70,72,73]

While interleaving TMS with fMRI is technically challenging, offline studies in which TMS is given before or after an fMRI session are easy to perform because TMS can be given outside the room where fMRI is performed.

Neuroscientific and clinical applications

Concurrent TMS-fMRI holds great promise to supplement our understanding about the immediate and rapid changes TMS can evoke in cortical networks.[74] One way is to use TMS-fMRI in a "perturb-and-measure" approach[75] that can inform about the activity changes evoked by TMS at a systems level, by characterizing TMS-evoked BOLD-signal changes throughout the brain at rest.[60,76-80] Here, TMS serves as a causal input into the operation of a cortical region, whereas fMRI measures distributed activity changes evoked by this input. This is of interest as one can in principle now reveal the spatial topography of TMS effects at high-spatial resolution, including retinotopic early visual cortex[81] and subcortical structures.[78,80] In the motor[60,76-80] and visual systems,[73,81] this has revealed that even short TMS pulse series (500 milliseconds-10 seconds) can activate putatively interconnected cortical and subcortical brain regions ipsilaterally and contralaterally to the stimulation site.

Furthermore, TMS-fMRI can disclose how such remote TMS-induced activity changes interact with psychologic factors such as task-state.[70] Increasing evidence suggests that the effects of TMS are dependent on the state of activation at the time of stimulation. Recently, Bestmann et al[70] could show that the effects of short trains of TMS (11 Hz, 5 pulses) applied to left dorsal premotor cortex (PMd) reversed during performance of a weak left-hand power grip, compared to rest (Figure 3). During rest, TMS applied at a suprathreshold intensity decreased contralateral primary motor cortex and PMd activity, compared with a low-subthreshold intensity. By contrast, stimulation at the suprathreshold intensity increased task-related activity in these regions during power grip, compared with low-intensity stimulation. This finding illustrates how concurrent TMS-fMRI can map out causal interactions among brain regions and their dependence on activation state.

Online fMRI has also been successfully established in conjunction with TES, in which a strong rapidly varying electric current rather than a time varying magnetic field is applied to stimulate cortical neurons.[18,19] Single suprathreshold electrical stimuli induced a positive BOLD response both in the ipsilateral as well as in the homotopic contralateral M1-HAND, with the latter presumably resulting from transcallosal connections. Accordingly, when a contralateral conditioning stimulus preceded the test stimulus by 10 milliseconds (interhemispheric inhibition), the subsequent ipsilateral BOLD signal was significantly reduced.[19] Thus, cortical inhibitory processes are accompanied by attenuation of the local neurovascular signal. TES during fMRI has the advantage that there are no spatial constraints when placing the stimulating electrodes. In contrast, placing a bulky TMS coil between the head and the MRI head coil is often problematic because of space limitations. A major drawback of combining TES with fMRI is that TES is more painful relative to TMS.

Concurrent TMS-fMRI has also been successfully applied to measure the distribution of activity changes during behavioral studies,[82] causal top-down influences between brain regions in the visual system,[73,81] sensory processing,[83] as well as the cortical signatures of an TMS-evoked sense of movement after upper limb amputation.[84] These findings suggest that attributing the behavioral consequences of TMS to the stimulation site often neglects remote activity changes induced by TMS and their contribution to possible behavioral consequences. Concurrent TMS-fMRI can reveal how these behavioral consequences

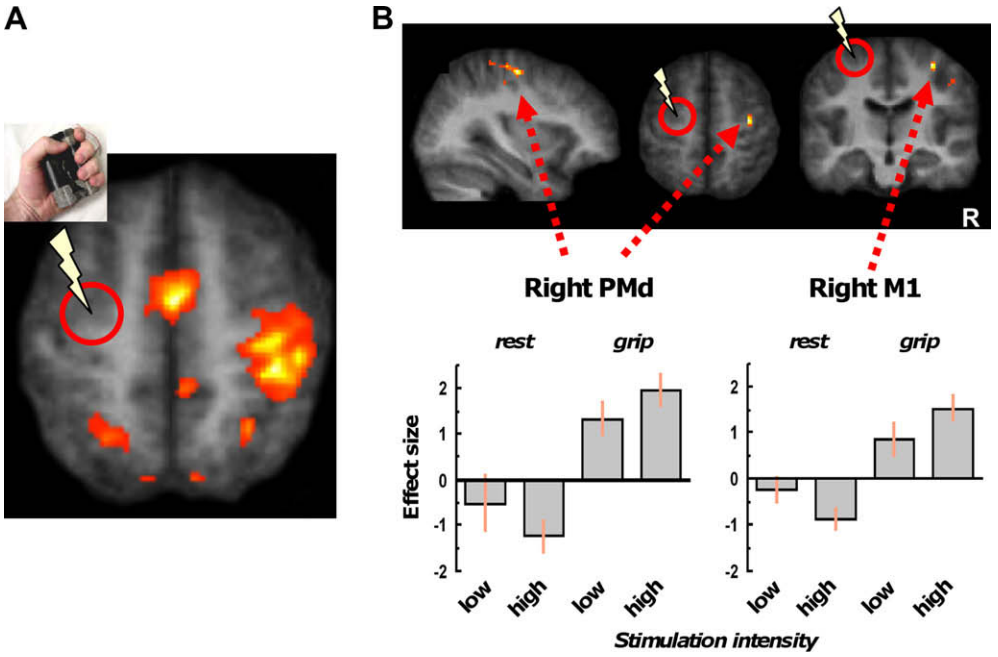

Figure 3 State-dependent interregional interactions evoked by transcranial magnetic stimulation (TMS) **(A)** Main effect of left hand grip, irrespective of TMS stimulation intensity. This illustrates how one can obtain blood-oxygenation-level-dependent (BOLD) activation maps during concurrent application of TMS pulses (5 pulses, 11 Hz) inside an magnetic resonance image (MRI) scanner. **(B)** Task-state dependent effects of TMS on causal interactions in the human motor system. At rest, TMS applied to the left dorsal premotor cortex (PMd) increased activity in contralateral PMd and primary motor cortex (M1) at high stimulation intensity (110% of resting motor threshold), compared with stimulation at a lower control intensity (70% active motor threshold). By contrast, this effect was reversed during a simple motor task that activated right PMd and M1. Now high-intensity stimulation increased task-related activity, compared with lower intensity stimulation. The results show how TMS can causally affect activity in contralateral regions, and that these influences are dependent on the activation state of these regions (adapted from Bestmann et al[70,72]).

emerge through concerted causal interplay among interconnected brain regions; alternatively, concurrent TMS-fMRI can show rapid compensatory activity changes that may prevent behavioral perturbation. Therefore, another exciting prospect of concurrent TMS-fMRI is to study the capacity of the brain to rapidly react to perturbations (caused by TMS), owing to the degeneracy in cognitive anatomy.[85]

In general, these approaches provide unique insight into the physiologic underpinnings of TMS, and the interregional layout of causal interactions. For clinical applications of TMS, this may be of critical importance because their effectiveness is commonly inferred indirectly through an improvement of clinical symptoms. It is often unknown, however, whether TMS actually targets and affects the brain regions implied in a specific clinical symptom. Li et al[86] have used concurrent TMS-fMRI in chronically depressed patients to investigate the brain regions affected by stimulation of left dorsolateral prefrontal cortex (DLPFC), a region often linked to major depression. Not only was 1-Hz TMS associated with increased activity at the site of stimulation, but also affected putatively interconnected regions including the bilateral middle PFC, right orbital frontal cortex, and insula. This study demonstrates that TMS to DLPFC can indeed affect entire brain networks associated with depression. Concurrent TMS-fMRI therefore holds promise to identify the brain regions targeted by clinical TMS applications, and thereby to increase their safety and effectiveness as well as point out novel strategies for TMS therapy. Li et al[86] have also shown how the interleaved TMS technique can be used to assess the modulatory effects of medications. Healthy subjects were scanned with interleaved TMS-fMRI over motor cortex while they were on or off lamotrigine, an anticonvulsant. Predictably, there was less TMS-induced motor cortex activation when subjects were on medication. Paradoxically, the exact opposite pattern occurred when these same subjects were stimulated over the PFC. There, the lamotrigine caused an increase in TMS-induced prefrontal activation.[87]

There is also a substantial potential for offline TMS-fMRI studies. First, fMRI can be used to guide the coil placement in a subsequent behavioral TMS experiment (fMRI-guided TMS).[22] Second, fMRI can map the functional consequences of a conditioning rTMS session on neuronal activity across the whole brain.[88,89] For instance, offline fMRI has been successfully applied to examine short-term reorganization in the right PMd after 1-Hz rTMS to the left PMd.[17] Although rTMS had no effect on behavior, fMRI revealed increased activity in the right

PMd and connected medial premotor areas during action selection but not simple action execution. Because subsequent online TMS of the reorganized right PMd impaired action selection, it was concluded that the functional reorganization as revealed by fMRI played a causal role in maintaining behavior after an rTMS induced interference with neuronal processing in the left PMd.

Conclusion/Summary

The future of TMS critically relies on identifying its mechanisms of action across the brain in more detail. One promising approach is the combination of TMS and BOLD fMRI. In measuring causal interactions throughout the brain in healthy humans, TMS-fMRI can therefore address questions that otherwise would be difficult to approach. In addition to BOLD sensitive MRI, several groups have started to combine TMS with other MR techniques such as MR spectroscopy[90,91] or arterial spin labeling,[92] which will reveal further valuable insights into the impact of TMS on brain function.

Structural MRI

Basic methodology

There are various MRI sequences that provide different insights into brain structure. Conventional structural imaging protocols include T1-weighted, T2-weighted, diffusion-weighted, and proton-density scans. These different protocols result in different tissue contrast, allowing particular anatomic or pathologic features to be visualized more easily. In the clinical setting, for example, T2-weighted images are particularly sensitive to inflammation, such as acute multiple sclerosis lesions; diffusion-weighted scans are most sensitive to very early pathologic changes following stroke; whereas T1-weighted images provide optimal contrast between grey and white matter and are therefore commonly used to provide fine anatomic detail. In a research setting, novel protocols have been developed to provide even richer anatomic information. For example, quantitative mapping of the relaxation contrasts, T1 and T2, can now be achieved over the whole brain at reasonable resolution in a feasible time. Such parameters are sensitive to pathologic factors and to anatomic microstructure. Extensions to conventional diffusion-weighted imaging (DWI) include acquisition of greater numbers of diffusion directions, which allows measurement of the directional dependence, or fractional anisotropy (FA), of the diffusion signal. This is a useful property to measure as FA reflects white matter integrity, and is therefore sensitive to changes in development, ageing, and disease. In addition, in white matter fiber bundles, the principal diffusion direction corresponds to the principal fiber direction and therefore, by following these directional estimates through white matter, it is possible to reconstruct the path of fiber bundles, to perform "diffusion tractography."

Technical and safety aspects

Given that structural imaging techniques, on the whole, provide static information, there is no particular reason for acquiring simultaneous TMS and structural MRI data (in contrast to the situation with fMRI, for example). Yet, as an MRI scanner can actually image the magnetic field created by a TMS coil, Bohning et al[93] demonstrated that one could acquire a phase map of the magnetic field distortions caused by running a constant current through a TMS coil. This TMS phase map, with appropriate scaling, can then directly image the magnetic field of the TMS coil over the subject's anatomy. However, in general, researchers have tended to relate TMS effects to structural data acquired separately. Therefore, there are no major technical challenges raised by combining these techniques.

Generic methodologic issues arise over acquisition, analysis, and interpretation of structural MRI data. Typical approaches to processing T1-weighted structural data include voxel-based and tensor-based morphometry (VBM[94] and TBM,[95] respectively) analyses. The VBM/TBM data processing includes segmentation of images into different tissue types (grey matter, white matter, cerebrospinal fluid), smoothing of resulting partial volume estimates, coregistration of images into standard space, and statistical comparison of voxel density values (VBM) or voxel displacement vectors (TBM) across subjects. Each step of this process raises issues. For example, the size of the smoothing kernel will greatly influence sensitivity to effects of different sizes. A number of groups are now also running VBM-style analyses of diffusion parameters, most commonly FA, which can be correlated with, for example, behavioral measures or the size of TMS effects.[96-99] Interpretation of FA correlates should vary depending on whether effects are seen in white matter or grey matter, and whether this localization is consistent across subjects after normalization. It is therefore important that regions of FA correlation are carefully localized in individual subjects, or that alternatives to VBM, such as tract-based spatial statistics,[100] or tractography-based definition of regions of interest, are used.

DWI can also be combined with TMS by using the anisotropic conductivity information to inform models of the current spread induced by a TMS pulse.[36]

Neuroscientific and clinical applications

The relationship between neuroanatomy and neurophysiology is a fundamental issue in neuroscience and is of clinical relevance. Caused in part by recent technologic advances in MRI, the neurosciences have seen an explosion of studies relating brain structure to function, where function is often assessed via behavior. Behavioral measures of function, however, reflect the aggregate operation of multiple brain regions. By contrast, TMS enables researchers to probe the physiology of a specific brain region, or functional

interactions between regions, both during resting and particular cognitive states. Such physiologic indices may provide more sensitive and informative measures with which to compare structural measures.

TMS-EMG measures of primary motor cortical excitability have been shown to correlate with gross conventional MRI volumetric measures, such as white matter hyperintensity volume and ventricular volume.[101] The majority of studies relating TMS to structural measures, however, have used measures derived from DWI. Recent work indicates that individual differences in cortical excitability and functional connectivity are associated with normal variation in white matter integrity in healthy adults. Primary motor cortical excitability, for example, was shown to correlate positively with FA in white matter underlying primary motor and premotor cortex, as well as parts of the corona radiata, internal capsule, cerebral peduncles, and corpus callosum (Figure 4A),[99] suggesting a substantial corticocortical contribution to motor threshold variation in healthy adults. Paired-pulse TMS, giving a measure of physiologic connectivity between stimulated cortical regions, has been recently used to interrogate the microstructural correlates of functional connectivity in healthy adults.[96-97] In one study, resting-state physiologic connectivity between hand regions of the left and right primary motor cortex was correlated positively with FA in hand callosal motor fibers identified with combined fMRI and diffusion tractography, but not adjacent foot fibers (Figure 4B), demonstrating an impressive degree of selectivity even within subregions of the same fiber bundle.[97] In the only study to date testing the importance of cognitive context to these relationships, functional connectivity from PMd to contralateral primary motor cortex, specifically during an action selection task, was positively correlated with FA in white matter underlying the premotor and primary motor cortex, the corpus callosum, and the superior longitudinal fascicles (Figure 4C).[96] Moreover, diffusion tractography from these regions of correlation reproduced the specific parietal-dorsal premotor-contralateral premotor-motor networks predicted to mediate the physiologic effects by previous fMRI findings.

The potential power of this approach is also evident in a clinical setting, where longer central motor conduction time to both the hands and legs has been associated with reduced FA in motor, premotor, and corticospinal tract white matter in patients with amyotrophic lateral sclerosis (ALS) with and without clinical symptoms of upper motor neuron disease.[102] Moreover, the presence of MEPs and the degree of corticospinal tract FA asymmetry predict the extent of functional recovery in chronic stroke.[98] These findings highlight the potential complementary value of combining TMS with DWI in both clinical diagnosis and prognosis.

Conclusion/Summary

Combination of TMS and structural MRI provides powerful approaches for testing the relationship between structure and function in the human brain. This approach enables us to address questions relating to development, ageing, and individual differences, as well as providing measures that could have important clinical application.

PET

Basic methodology

PET maps the regional binding and metabolism of compounds that have been tagged with short-lived positron-emitting isotopes such as carbon-11, oxygen-15, or fluorine-18. The emitted positrons, when they annihilate with electrons, produce pairs of gamma rays that are detected by the PET scanner. The resulting PET images provide three-dimensional (3D) maps of the tracer distribution in tissue. PET offers a range of possibilities to study human brain function.[103] Using different radioactive tracers (radioligands), PET can quantify changes in regional cerebral blood flow (rCBF) or regional cerebral metabolic rate of glucose (rCMRglc).[104] Because rCBF and rCMRglc are tightly coupled with synaptic activity, PET imaging of regional blood flow or glucose metabolism provides an index of regional synaptic activity at rest and during specific tasks. Other radioligands can be used to examine specific neurotransmitter and receptor systems, or to map amino-acid uptake or microglial activation.[104,105] The radioisotope-based imaging technique with the highest resolution and greatest sensitivity to differentiate between normal and abnormal functional states is 3D PET. The most available technique, however, is single-photon emission computed tomography (SPECT). SPECT uses radioisotopes with a long half-life and does not require an on-site cyclotron. SPECT and PET are discussed together because the general issues regarding the combined use of SPECT and TMS are identical to those encountered when combining TMS with PET.

Technical and safety aspects

The most important drawback of PET and SPECT is the exposure to radiation. This limits the number of measurements that can be performed in human subjects. It also adversely affects the general acceptance of the method. Because radiation exposure is far less problematic in animals, serial PET measurements in animals are very useful to assess long-term effects of TMS on brain activity. In anesthetized monkeys, Hayashi et al[106] performed four ^{18}FDG-PET measurements before, during, as well as 8 and 16 days after 2000 stimuli of 5-Hz rTMS were applied over the right precentral gyrus. They found that the rTMS decreased rCMRglc in motor/premotor cortices, whereas rCMRglc in the anterior/posterior cingulate and orbitofrontal cortices was enhanced. Critically, these changes in regional

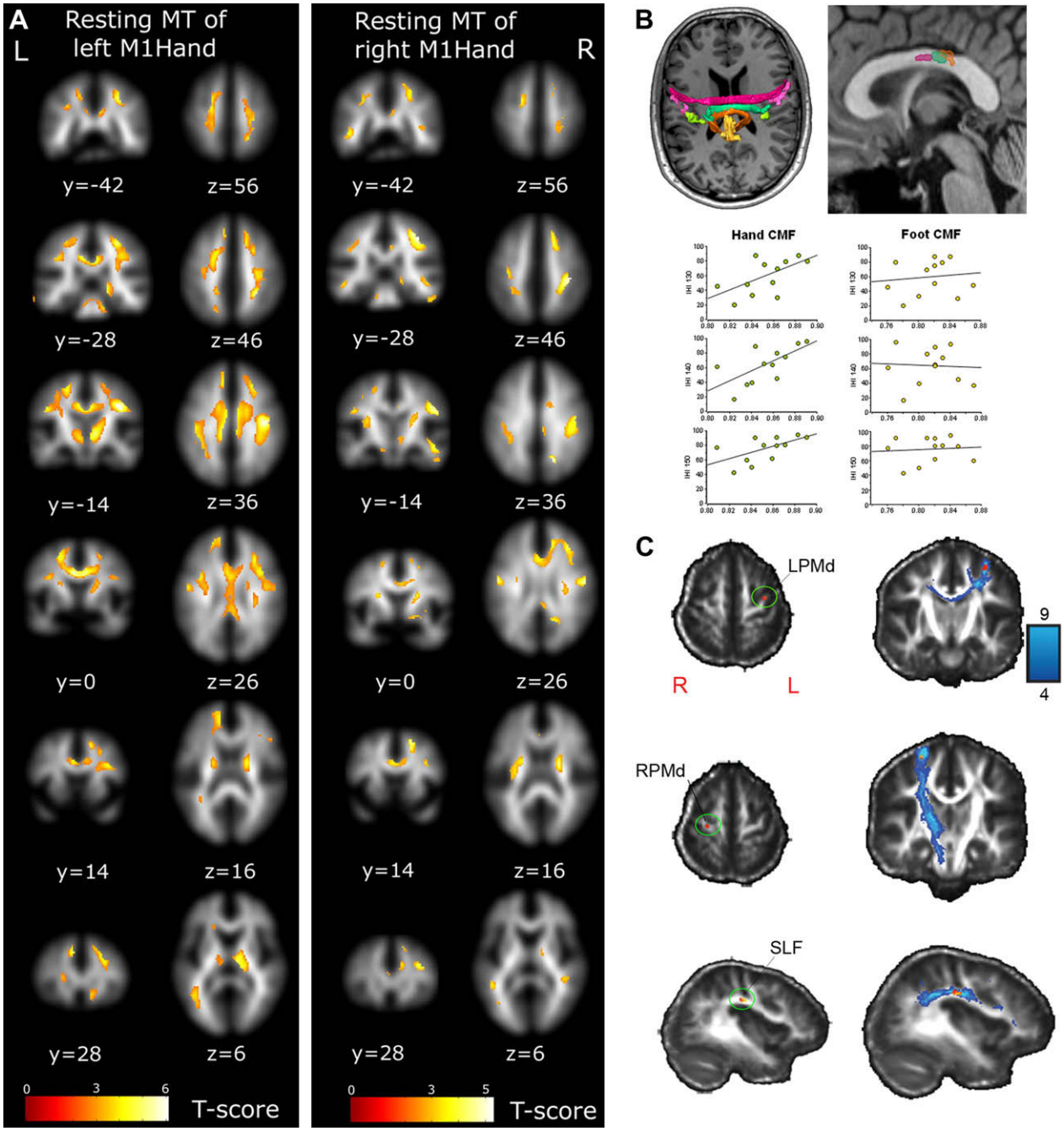

Figure 4 **(A)** Correlations between fractional anisotropy (FA) and primary motor cortical excitability (as measured by resting motor threshold) for left (left) and right (right) M1 (after Kloeppel et al[99]). **(B)** fMRI-defined M1 representations (lip: light red; hand: light green; foot: yellow) and tracked CMFs (lip: dark red; hand: dark green; foot: orange) visualized as three-dimensional objects in one subject (top). Hand but not foot FA measured from the midbody of CMFs correlated significantly with the degree of interhemispheric inhibition between the hand areas of M1 (bottom) (after Wahl et al[97]). **(C)** Local regions of correlation between functional connectivity from left dorsal premotor cortex (LPMd) to right M1 during action selection and FA in white matter underlying LPMd, RPMd, and the superior longitudinal fascilculus (SLF) (left column). Probabilistic diffusion tractography from the clusters of correlation demonstrating the white matter tracts in which local correlations were found and their gray matter targets (right column) (after Boorman et al[96]).

metabolism persisted for at least 8 days.[106] Such a longitudinal study would be impossible to perform in humans because of the excessive exposure to radiation.

No specific methodologic precautions are required if TMS is given outside the scanner before or after PET measurements (ie, offline TMS). TMS during PET (ie, online TMS) is also easy to establish. After initial concerns,[107] there is now consensus that the phasic magnetic field produced by each TMS pulse does not affect the function of the PET detectors.[108] The TMS coil on the

subject's head, however, attenuates the radiation that is picked up by the PET detectors. Therefore, it is necessary to acquire a transmission scan with the TMS coil in situ to correct for coil-induced signal attenuation during preprocessing. If two cortical areas are sequentially targeted during the same PET experiment, one needs to have separate transmission scans for each of the coil positions.

An advantage of the combined PET-TMS approach is that all currently available rTMS protocols can be given in the PET scanner since PET does not impose any temporal constraints on TMS. The PET environment imposes less spatial constraints to position the coil than MRI, rendering it possible to use frameless stereotaxy to place and monitor the coil position during online imaging.[109,110] Alternatively, correct coil position can be identified with frameless stereotaxy outside the scanner and marked on the subject's head. The coil can then be centered on the marked area after the subject has been positioned in the scanner. Correct placement of the coil can be verified on the transmission scan where the coil is clearly visible. The anatomic location of the coil can be determined by coregistering the transmission scan on the individual structural MRI scan.[110] In addition, a vitamin E capsule can be taped on the scalp under the center of the coil, and the correct placement of the coil can be confirmed with standard T1-weighted structural MRI after the end of PET measurements.

For target areas close to the central sulcus, the TMS-induced motor response can alternatively be used to localize the primary motor cortex, which can be used as a reference area to locate somatosensory or premotor areas.[15] Some groups have also used the international 10-20 system for placement of EEG electrodes to localize the site of TMS. A drawback of this approach is that the 10-20 system does not take into account interindividual differences in cortical anatomy. In addition to correct coil placement, it is essential to ensure a constant coil position during consecutive PET measurements. A mechanical or robotic fixation unit should be integrated in the bore of the PET scanner for positioning and fixating the coil over the cortical target area. In addition, coil position should be checked between consecutive PET measurements.

Neuroscientific and clinical applications

Most studies combined TMS with PET techniques that measure regional synaptic activity over several tens of seconds ($H_2{}^{15}O$-PET of rCBF) or minutes (^{18}FDG-PET of $rCMR_{glc}$). Because of its low temporal resolution, continuous train or intermittent bursts of rTMS need to be given to induce a detectable change in regional neuronal activity. A single PET scan always represents the cumulative effects of individual stimuli on regional synaptic activity during the period of measurement. This feature defines the strength and weakness of the combined TMS-PET approach: On the one hand, the combined TMS-PET approach is not suited to examine the effects of a single pulse or a short train of TMS on regional neuronal activity. On the other hand, combined TMS-PET measurements can readily probe cumulative changes in regional neuronal activity in the stimulated cortex and connected brain regions during rTMS because the neuronal effects of each stimulus can sum up during a single PET scan.

TMS can be applied during concurrent PET measurement of regional neural activity to visualize immediate effects of TMS on regional synaptic activity in the stimulated cortical area and connected brain regions. PET of rCBF or rCMRglc during the administration of TMS can map immediate TMS-induced changes in regional activity and connectivity independent of behavior. This "online" approach has been successfully used to assess how TMS-induced changes in neuronal activity depend on the intensity, frequency, or site of TMS.[109-114] Most studies examined the acute effects of TMS on rCBF or rCMRglc while participants were at rest, but online TMS-PET imaging can also be used to examine how focal TMS interacts with the regional activation pattern during a specific task.[115,116]

Although early TMS-PET studies focused on acute effects on rCBF or rCMRglc produced during TMS, more recent studies examined how rTMS shapes regional neuronal activity in the human brain beyond the time of TMS. Serial PET measurements of rCBF can track the time-course of functional after effects induced by rTMS both at rest and during a task.[16,117] A $H_2{}^{15}O$-PET study showed that 1-Hz rTMS given at an intensity of 90% resting motor threshold to left primary motor cortex (M1) caused bilateral increases in regional neuronal activity in primary motor and premotor cortices and cerebellum relative to sham rTMS.[16] The same 1-Hz rTMS protocol applied to left PMd yielded bilateral decreases in activity (compared with sham rTMS) in primary motor, premotor, prefrontal, and subcortical areas.[15] Changes in rCBF persisted for at least 1 hour after the end of rTMS, showing that rTMS can produce lasting effects on regional neuronal activity in the stimulated cortex and connected brain regions.

From measurements of the MEP, it is known that 1-Hz rTMS to M1 or PMd can reduce the amplitude of MEPs elicited in the conditioned M1. Despite of similar suppressive effects on corticospinal excitability, the PET measurements revealed marked differences in the effects of 1-Hz rTMS over M1 or PMd on regional neuronal activity. Two PET studies examined changes both in cortical excitability (by measuring MEPs) and in regional neuronal activity (by measuring rCBF) in response to focal rTMS.[118,119] Chouinard et al[118] correlated changes in MEP amplitude after 1-Hz rTMS to M1 or PMd with changes in rCBF before and after rTMS. They identified a number of brain regions in which decreases in MEP amplitude were associated with increased rCBF after rTMS. The regional patterns of correlations differed according to whether rTMS had been given to PMd or M1. Taken together, these results provide

converging evidence that the after effects of rTMS critically depend on the site of rTMS. They also highlight that it is problematic to draw simple parallels between changes in overall regional neuronal activity (as indexed by rCBF) and electrophysiologic tests of neural excitability (as indexed by the amplitude of the MEP).

Another line of research used rTMS to induce acute reorganization in functional brain networks. Several PET studies have shown that rTMS has lasting effects on task-related regional activity and interregional coupling during a given task.[16,120] Lee et al[16] reported marked changes in functional brain activity after 1-Hz rTMS of left M1 in the absence of any overt behavioral change. Movement-related activity increased in the right PMd and the inferomedial portion of the left M1 along with increased coupling between the inferomedial M1 and premotor areas during movement. These changes indicate rapid compensatory reorganization within the motor system that may help to maintain functional integrity. It was proposed that these acute reorganization patterns may be analogous to plastic changes associated with natural recovery of function after brain injury.[16] Lasting changes in interregional connectivity can also be tested by applying focal rTMS to a cortical area and subsequently probing the responsiveness of the stimulated network with online PET during focal TMS. A conditioning session of 10-Hz rTMS applied to the mid-DLPFC modulated the acute response of the frontocingulate circuit to TMS.[121]

Only a relatively small number of studies have used the combined TMS-PET approach in patients, mainly to examine the therapeutic effects of repeated sessions of prefrontal rTMS on rCBF and rCMRglc as a treatment for depression,[122-125] as introduced by George et al.[126] These studies show that serial metabolic PET or SPECT studies provide important insights into the mechanism of action of rTMS in patients and may help to predict antidepressant efficacy of different stimulation paradigms. The combined TMS-PET approach can also shed new light on the pathophysiology of neurologic and psychiatric disorders. For instance, patients with focal hand dystonia showed a greater suppression of regional synaptic activity in lateral and medial premotor areas, putamen, and thalamus after 1-Hz rTMS of left PMd, indicating enhanced plasticity of the corticobasal gangliathalamic loop in focal hand dystonia.[15]

Finally, PET provides the unique opportunity to investigate the effects of TMS on specific neurotransmitter systems (eg, the dopaminergic system) or cell populations (eg, the microglia). In healthy volunteers, ^{11}C-raclopride PET was used to measure changes in extracellular dopamine concentration after high-frequency rTMS of the left DLPFC[127] or the M1.[128] Focal rTMS to the DLPFC and M1-HAND led to spatially restricted decreases of ^{11}C-raclopride binding in ipsilateral corticostriatal projection zones of the stimulated cortical area. This regionally specific decrease in ^{11}C-raclopride binding potential indicates that focal rTMS can induce a lasting increase in endogenous dopamine release in the corresponding striatal projection zone, presumably through repetitive stimulation of corticostriatal connections during rTMS.

The rTMS/^{11}C-raclopride PET methodology offers the opportunity to investigate corticostriatal functional interactions in neurologic and psychiatric diseases. In fact, abnormalities in corticostriatal interactions are believed to play an important role in the pathophysiology of Parkinson's disease (PD).[129] The evidence of a spatially enlarged area of dopamine release in the symptomatic hemisphere after M1-TMS/^{11}C-raclopride PET may represent a possible in vivo expression of a loss of functional segregation of cortical information to the striatum and an indirect evidence of abnormal corticostriatal transmission in early PD.[129] Investigations of corticostriatal transmission have also been described in psychiatric conditions such as primary depression using SPECT[130,131] as well as in different animal models.[132-135] Ever since the adoption of rTMS as a research tool, there has been great interest regarding its potential clinical role. To date, studies addressing the contribution of placebo during TMS are limited. The placebo effect has been shown to be associated either with release of dopamine in the striatum.[136] Recently, Strafella et al[137] showed in patients with PD that expectation of therapeutic benefit from sham rTMS (placebo-rTMS) induced a diffuse, bilateral reduction in [^{11}C] raclopride BP (ie, release of dopamine) in dorsal and ventral striatum.[137] These observations confirm earlier evidence that expectation of clinical benefit (either from drugs or medical devices) induces significant dopaminergic placebo effects suggesting the importance of placebo-controlled studies for clinical trials involving brain stimulation techniques.

Conclusion/Summary

The combined use of TMS and PET has considerably expanded the applications of TMS in basic neuroscience and clinical research. The existing data convincingly show that online PET during TMS provides a behavior-independent assay of cortical excitability and connectivity. Offline PET after a conditioning session of rTMS provides a valuable means to investigate how rTMS shapes regional neuronal activity in the intact human brain. In recent years, several new protocols of rTMS have been introduced which consist of repeated bursts or paired stimuli.[9] Here, offline PET will be of great value to compare the topographic and temporal profiles of changes in regional activity produced by various rTMS protocols. As such, offline PET imaging can make an important contribution to the understanding of the mechanisms of action of rTMS. A unique strength of the combined TMS-PET is to map the effects of rTMS on regional neurotransmission. Although PET has only been used to map TMS-induced changes in dopaminergic neurotransmission, it would be very helpful to extend this approach to other neurotransmitter systems, including the serotoninergic and cholinergic system. Other

interesting extensions of the TMS-PET approach include the use of PET ligands that label activated microglia or amyloid deposits.

Near infrared spectroscopy

Basic methodology

Near infrared spectroscopy (NIRS) is a spectroscopic method measuring the wavelength and intensity of the absorption of near-infrared light by the tissue. NIRS can be used to probe brain function through the intact skull by detecting changes in blood hemoglobin concentrations associated with neural activity. Devices designed to estimate blood gas levels in the brain commonly use the light within the lower near infrared spectrum rather than visible light because of its greater penetration through the scalp. NIRS measures tissue absorbance and scattering of light at two or more wavelengths in the spectral region from 700-1000 nm, thus enabling the determination of concentration changes of oxygenated hemoglobin (oxy-Hb), deoxygenated hemoglobin (deoxy-Hb), and blood volume (total-Hb; oxy-Hb + deoxy-Hb) using mathematical models based on the modified Lambert-Beer law.[138]

Technical and safety aspects

Instrumentation for NIRS consists of a source (transmitter) that emits infrared light into the tissue, a detector (receiver) and a dispersive element (eg, a prism or a diffraction grating) to allow the intensity at different wavelengths to be recorded. A distance of each pair is adjusted to about 3 cm, which is suitable for detecting the Hb concentration at the cerebral cortex and reducing the influence of skin Hb changes.[139] Conventional NIRS has been limited to measurements from a few specific sites. Recent technologic advances enable to perform NIRS simultaneously from multiple sites and to display the results of multisite NIRS as cortical maps.

NIRS can be used to visualize the effects of TMS on cortical activity.[140] The NIRS method has several advantages over other neuroimaging techniques. It has a high signal-to-noise ratio. NIRS can be performed while TMS is being applied because the time-varying electromagnetic field induced by the TMS pulse does not interfere with NIRS. NIRS can be used in newborns and infants because of the lack of any side effects. NIRS devices are portable, enabling investigations in freely moving subjects.[141] Furthermore, NIRS has a temporal resolution that is comparable to fMRI.

There are also several limitations: The technique has a relatively poor spatial resolution when compared with fMRI. Because of the limited depth penetration of the infrared light, NIRS can only probe activity in superficial cortical regions. Because NIRS is highly sensitive to fluctuations in the light intensity of the environment, recordings need to be performed in a slightly darkened room and repeated at least 10 times. Trials need to be averaged to obtain stable results.

Although TMS has been successfully combined with NIRS, several issues remain to be solved. The placement of the probe interferes with the placement of the coil, increasing the distance between the TMS coil and the cortical target region. There is still some debate which wavelengths should be preferentially used and how strong lights should be used in combined TMS-NIRS studies. Another problem is that NIRS is difficult to perform in individuals with black hair. It is possible to record good responses in these subjects by increasing the intensity of the light that is emitted in the tissue. However, the safety guidelines for light exposure may limit the possibility to increase the intensity of the emitted infrared light, especially when studying children or infants. Finally, head movements induced by the vibration of the stimulating coil may sometimes disturb a good recording because of the movements of the NIRS probes in simultaneous NIRS-TMS studies.

Neuroscience and clinical applications

During physiologic brain activation (eg, in response to a sensory stimulus), NIRS typically shows a large oxy-Hb increase along with a small deoxy-Hb decrease.[138] If a region is deactivated, this is reflected by NIRS as an decrease in oxy-Hb and an increase in deoxy-Hb.[142] Only a few studies combined NIRS recordings with TMS. Interestingly, Hb concentration changes evoked during or after TMS appear to be different from the normal physiologic response profile. The first study that combined TMS and optical imaging reported a right-hemisphere response when the left motor cortex was stimulated.[143] The first study with two wavelengths reported local changes in Hb concentration just beneath the coil.[144] A significant increase in oxy-Hb was observed after single-pulse TMS (90% or 110% active motor threshold) when the subjects voluntarily contracted a target hand muscle. This spectroscopic response was similar to the physiologic activation pattern. On the other hand, single-pulse TMS (120% or 140% active motor threshold) induced large deoxy-Hb decreases and no significant oxy-Hb changes when the contralateral target muscle was relaxed.[145] This atypical response pattern may be explained by TMS-induced changes in the intrinsic firing rate of cortical and corticospinal neurons because of the lasting inhibition provoked by high-intensity TMS.

NIRS has also been used to measure regional changes in Hb concentration in the right PFC, PMd, M1-HAND, and primary sensory hand area (S1-HAND) during and after intermittent theta burst rTMS over the left PMd, M1 and S1, or sham stimulation. Intermittent theta burst rTMS over premotor or sensorimotor cortices induced large oxy-Hb

decrease and small deoxy-Hb increase (deactivation pattern) in the premotor or sensorimotor cortices contralaterally to the site of rTMS.[146] In another study,[147] NIRS recording was performed over the left M1-HAND during right-hand finger tapping before and after 1-Hz rTMS of the right M1-HAND. The 1-Hz rTMS of the right M1-HAND increased the level of oxy-Hb in the nonstimulated cortex for 40 minutes after the end of rTMS. Deoxy-Hb was found to be slightly decreased during the first 15 minutes after rTMS. These results confirm that 1-Hz rTMS of one hemisphere can produce persisting changes in cortical function in homologous regions of the nonstimulated hemisphere.

Conclusion/Summary

NIRS is a highly interesting method to assess the acute effects of TMS on cortical function because the spectroscopic measurements are not perturbed by concurrent TMS. Yet, there are still several problems to be solved before it will be possible to fully exploit the potential of NIRS for online TMS studies.

General conclusion and perspectives

The combined use of TMS with other brain mapping techniques has greatly expanded the scientific potential of TMS in basic neuroscience and clinical research. The offline and online TMS-neuroimaging approaches offer complementary applications. Online neuroimaging during the administration of TMS provides a behavior-independent assay of the functional brain response of the stimulated cortex as well as connected cortical and subcortical brain regions. Major progress has been made in solving technical problems caused by the interfering effects of TMS on data acquisition in concurrent TMS-fMRI and TMS-EEG studies. It remains a challenge, however, to optimize experimental approaches in a way that it is possible to disentangle the direct effects in the brain caused by TMS from nonspecific neuronal effects in response to associated auditory and somatosensory stimulation. A very promising avenue of research that can be pursued in online TMS-neuroimaging experiments is to systematically modulate the functional state of the stimulated cortex and connected brain regions at the time of stimulation (eg, by changing the behavioural context) and assess how distinct changes in functional state of the brain at the time of TMS impacts on the brain response to TMS. This offers new possibilities to probe effective connectivity in vivo. The online TMS-neuroimaging approach also allows us to explore how focal TMS interferes with task-related activity when given to different cortical regions or at different time points during a behavioral task. We anticipate that this approach will yield important insight into the mechanisms that mediate the disruptive effect of TMS on neuronal processing.

While online TMS-neuroimaging is technically demanding and requires specific safety precautions, the offline TMS-neuroimaging approach can be easily performed because TMS and neuroimaging are separated in time and possibly in space. Neuroimaging studies can be exploited to guide the timing and placement of TMS in studies that use TMS during experimental tasks to modify behavior. In addition, offline TMS-neuroimaging offers a powerful tool for investigating the neuromodulatory effects of rTMS. It provides unique opportunities to explore dynamic aspects of functional brain networks on spontaneous and task-related activity in space and time and how these functional interactions are affected by disease. As such the offline TMS-neuroimaging approach bears great potential for studying the brain's capability to undergo short-term reorganization in health and disease.

There is no general answer to the question which functional neuroimaging modality is best to use in conjunction with TMS. The previous sections show that each neuroimaging technique offers complementary information and is associated with different methodologic strengths and weaknesses. The selection of the neuroimaging technique should be tailored to the scientific question, taking into account which aspects of neuronal function are captured by a given neuroimaging technique along with its spatial and temporal resolution.

Combining TMS with structural neuroimaging is yet another promising avenue of research. One way to exploit structural neuroimaging is to correlate electrophysiologic measures of cortical excitability or corticocortical connectivity (as obtained with TMS) with measures of regional brain structure. Correlational analysis may alternatively test for relations between TMS-induced behavioural effects and neuroimaging measures of regional brain structure. Another application includes the morphometric assessment of changes in brain structure following the repeated application of rTMS over multiple sessions.[148]

Future extensions include the use of new imaging modalities such as resting-state fMRI, MR spectroscopy, or molecular PET imaging that use markers of activated microglia or amyloid deposits. Neuroimaging will also be key to better characterize and compare the impact of newly developed conditioning protocols on brain function and structure, including theta burst stimulation,[149] corticocortical paired associative stimulation,[150] or transcranial direct current stimulation.[151] Finally, combined TMS-neuroimaging studies in patients will be instrumental in clarifying the therapeutic effects of rTMS and will provide substantial new insights in the pathophysiology of neurologic or psychiatric diseases.

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