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Transcranial magnetic stimulation and connectivity mapping: tools for studying the neural bases of brain disorders

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There has been an increasing emphasis on characterizing pathophysiology underlying psychiatric and neurological disorders in terms of altered neural connectivity and network dynamics. Transcranial magnetic stimulation (TMS) provides a unique opportunity for investigating connectivity in the human brain. TMS allows researchers and clinicians to directly stimulate cortical regions accessible to electromagnetic coils positioned on the scalp. The induced activation can then propagate through long-range connections to other brain areas. Thus, by identifying distal regions activated during TMS, researchers can infer connectivity patterns in the healthy human brain and can examine how those patterns may be disrupted in patients with different brain disorders. Conversely, connectivity maps derived using neuroimaging methods can identify components of a dysfunctional network. Nodes in this dysfunctional network accessible as targets for TMS by virtue of their proximity to the scalp may then permit TMS-induced alterations of components of the network not directly accessible to TMS via propagated effects. Thus TMS can provide a portal for accessing and altering neural dynamics in networks that are widely distributed anatomically. Finally, when long-term modulation of network dynamics is induced by trains of repetitive TMS, changes in functional connectivity patterns can be studied in parallel with changes in patient symptoms. These correlational data can elucidate neural mechanisms underlying illness and recovery. In this review, we focus on the application of these approaches to the study of psychiatric and neurological illnesses.

Keywords: transcranial magnetic stimulation, connectivity, psychiatry, neurology, brain disorders, resting, stimulation

INTRODUCTION

Transcranial magnetic stimulation (TMS) allows focal, non-invasive stimulation of the human brain using very brief duration magnetic waves administered by an electromagnetic coil positioned on the scalp. Stimulation coils typically generate magnetic field pulses of approximately 1.5–2 T that pass relatively undistorted through the scalp and skull (George et al., 1999). Rapidly oscillating magnetic fields within the brain induce corresponding electrical fields, which stimulate underlying gray matter. A standard figure-8 configured coil achieves relatively focal direct stimulation with a 2–2.5 cm diameter spread at the cortical surface under the crossing of the figure-8, while a circular coil delivers a wider spread of stimulation (Cohen et al., 1990). Direct neural activation is achieved up to ~2 cm from the surface of the magnet (Rudiak and Marg, 1994), which is sufficient to reach the gray/white interface of cortex adjacent to skull. The exact nature of neural effects induced by TMS is not known, but complex, enduring changes in spontaneous and evoked activity and synchronization of neural firing have been shown to be induced when administered to the cat visual cortex (Allen et al., 2007). Overall, TMS has proved to be relatively safe with a few cases of seizures associated primarily with repetitive stimulation at higher frequencies (i.e., 10 Hz or above, Wassermann, 1998; Rossi et al., 2009). Although momentary virtual "lesions" can be induced by TMS that are detectable via neuropsychological methods (Walsh and Rushworth, 1999), sustained cognitive disturbances induced by TMS in humans have not been observed (Pascual-Leone et al., 1993; Rossi et al., 2009).

Excellent reviews of TMS from the perspectives of neuropsychology (Walsh and Rushworth, 1999), psychiatry (George et al., 1999) neurology (Rossini and Rossi, 2007) and safety (Rossi et al., 2009) have been published. In this review, we focus primarily on approaches in which connectivity mapping and TMS can be used in conjunction to study neurological and psychiatric disorders in order to provide a sense of the more common available techniques and examples of these approaches. By connectivity mapping, we mean imaging techniques that assess connectivity between distal brain areas, such as functional connectivity analyses and diffusion tensor imaging. Thus, we focus primarily on TMS studies of inter-regional, rather than intraregional, connectivity.

Another form of non-invasive brain stimulation, transcranial direct current stimulation, or tDCS, can produce changes in brain excitability that can persist for a period of time after stimulation (Priori, 2003). To date, this technology has been less extensively used in conjunction with connectivity mapping, and will not be covered in this review except to note that several recent papers have reported that tDCS may modulate distal brain areas via inter-regional connectivity (Boros et al., 2008; Galea et al., 2009; Stagg et al., 2009).

TYPES OF STIMULATION

There are two broad classes of stimulation paradigms for TMS: single/paired/triple-pulse paradigms, and repetitive stimulation paradigms.

SINGLE/PAIRED/TRIPLE-PULSE

Single pulse TMS can be used to interfere with activity in the stimulated region, and thus to act as a temporary lesion. By applying such pulses at different times and to different regions, and examining the behavioral consequences, the roles of different regions in a cognitive process, and their temporal dynamics, can be studied (Terao et al., 1998; Zangaladze et al., 1999). A single pulse does not always have an inhibitory effect on a region: in some cases, facilitatory effects have been reported (Grosbras and Paus, 2002). However, the temporal profile of such facilitatory effects can also be informative.

Paired-pulse paradigms can be used to investigate interactions between motor or visual regions of the brain. When applied to the primary motor cortex (M1), a single pulse can induce a motor evoked potential (and the corresponding body movement), and when applied to the primary visual cortex (V1), the perception of a phosphene can be induced. The response elicited by a single pulse (that is, the motor evoked potential or phosphene) can be modulated by the application of preceding pulses in the same, or a connected brain region in a manner dependent on the temporal relationship of the pulses. In this fashion, paired pulses, that is, a conditioning pulse followed by a test pulse, can be used to examine connectivity and cortical dynamics in the motor and visual systems.

More complex aspects of cortical dynamics can be studied with triple-pulse paradigms. The effect of a conditioning pulse on a subsequent test pulse can be altered by preceding them both with an earlier pulse. Paradigms like this have been used to investigate the possible cellular mechanisms underlying different forms of intracortical inhibition and facilitation (Sanger et al., 2001) and to investigate how intracortical dynamics affect interregional interactions (Koch et al., 2007).

REPETITIVE TMS

Repetitive stimulation typically involves short trains of high-frequency stimulation (≥5 Hz) or long trains of low-frequency stimulation (≤2 Hz) applied at a single site. Low-frequency stimulation typically results in depression of the target brain area for a period of time following stimulation, while high-frequency stimulation typically induces facilitation of the region (Pascual-Leone et al., 1994; Chen et al., 1997; Speer et al., 2000). However, one particular high-frequency stimulation paradigm, referred to as theta burst stimulation, can produce either inhibitory or facilitatory effects that extend for many minutes after stimulation (Huang et al., 2005). This paradigm involves short bursts of very high-frequency stimulation (3 pulses at 50 Hz) repeated at 200 ms interval (which corresponds to the 5 Hz theta frequency). If the stimulation pattern is applied continuously, facilitatory effects are produced, but when applied intermittently (2 s trains repeated every 10 s), inhibitory effects can result.

Repetitive TMS (rTMS) has been investigated as a treatment for a variety of psychiatric illnesses. By examining behavioral, clinical, or cognitive changes before and after rTMS, repetitive stimulation can also be used in basic research to study how perturbations in activity in a focal brain area affect the network function.

INVESTIGATING CONNECTIVITY WITH TMS ALONE

Single-pulse TMS paradigms can, in some scenarios, provide information regarding connectivity in the human brain. The excitability of the primary motor and visual cortices can vary depending on the cognitive context in which stimulation occurs, and this dependence on cognitive state provides a window into the connectivity between these areas and cognitive regions. For example, during some language tasks, the motor cortical hand area in the language dominant hemisphere of healthy subjects is more excitable, as reflected by larger motor evoked potentials recorded following TMS (Tokimura et al., 1996; Meister et al., 2003). This finding provides evidence of functional connectivity between the hand area of motor cortex and language areas in healthy subjects, and allows investigation of the integrity of these connections in patient groups. In patients with mild cognitive impairment, for example, language tasks were shown to have a reduced effect on motor cortex excitability, suggesting decreased connectivity between motor and language areas in this patient group (Bracco et al., 2009). In patients recovering from post-stroke aphasia due to a dominant hemisphere lesion, the motor cortical hand area in the right (non-dominant) hemisphere was found to be more excitable during reading aloud, suggesting a reorganization of language function with greater recruitment of right hemisphere circuitry (Meister et al., 2006).

Paired-pulse paradigms using two sequential pulses provide an alternative and more spatially focused approach to probing interregional connectivity. The first pulse is referred to as the conditioning stimulus, and the second is referred to as the test stimulus. The latter is applied to a region with an observable output response. Typically, primary motor cortex (M1) receives the test stimulus, and motor evoked potentials are recorded in the affected muscles. By applying a preceding conditioning stimulus to another motor area and measuring how it affects the motor potentials induced by the test stimulus, connectivity between the region receiving the conditioning stimulus and M1 can be probed (Civardi et al., 2001). Individual differences across subjects in specific connections to M1 can be estimated in this manner and correlated with subject variables such as personality dimensions (Hofman and Schutter, 2009) in order to gain greater insight into the role of those specific connections in mental function.

A variety of creative paradigms have been adopted using paired pulse stimulation to examine connectivity in the motor system and its role in behavior. For example, it has been reported that a conditioning stimulus to the ventral premotor cortex during grasp preparation facilitates motor evoked potentials (in response to M1 stimulation) in the muscles specific to the grasp prepared (Davare et al., 2009). This supports the view that ventral premotor cortex contains populations of neurons that exert grasp-specific facilitatory influences on M1. Another study examining excitation of the hand area of M1 during foot movements revealed that dorsal premotor cortex influenced the hand region of M1 in a manner that facilitated isodirectional hand and foot movements (Byblow et al., 2007). Paired-pulse paradigms have revealed aberrant patterns of connectivity to primary motor cortex associated with disorders that have long been hypothesized to involve dysfunctional connectivity, such as schizophrenia and epilepsy (Daskalakis et al., 2005; Loscher et al., 2007; Koch et al., 2008a; D'Argenzio et al., 2009).

Triple-pulse paradigms can probe more complex relationships. For example, a study of interactions between dorsal premotor cortex (which was stimulated with a pair of pulses) and contralateral M1 (which received a single pulse) in focal arm dystonia failed to reveal the usual pattern of interaction between pairs of premotor stimuli (Koch et al., 2008b). Thus, disrupted intraregional dynamics in premotor cortex may play a role in the aberrant influence premotor cortex exerts on M1 in this disorder.

To a lesser extent, connectivity in the visual system has also been probed using paired-pulse paradigms. For example, although in healthy subjects, a conditioning stimulus to MT/V5+ does not modulate the perception of phosphenes in contralateral V1, in a patient with a unilateral V1 lesion, a conditioning stimulus to MT/V5+ in the damaged hemisphere did modulate phosphenes induced by a test stimulus to V1 in the intact hemisphere (Silvanto et al., 2009). This finding was consistent with prior reports of increased connectivity between right and left MT/V5+ in that patient.

In summary, using a variety of experimental designs in which the context is modified, single, paired, and triple-pulse TMS paradigms can be effective tools for probing connectivity in the motor and visual systems in both healthy and patient populations. However, these paradigms are limited to studying connectivity to regions with overt responses (that is, M1 and V1). In order to study connectivity between other regions of the brain, paradigms combining TMS with other imaging modalities are utilized.

INVESTIGATING CONNECTIVITY PATTERNS BY COMBINING TMS WITH IMAGING

Transcranial magnetic stimulation can be used in conjunction with a variety of brain imaging technologies to map connectivity patterns in the human brain. A site is stimulated, and the subsequent activation occurring in distal areas is assessed. Such data can provide information on connectivity patterns. If propagated activation is assessed using electrophysiological methods, conduction delays can also be estimated. However, it is important to remember that physiological propagation of activation between brain regions under natural conditions may not be precisely reflected by the patterns elicited during TMS, which stimulates the brain in a highly unnatural manner. Despite this caveat, the combination of TMS with brain imaging can be very useful in probing brain systems.

Transcranial magnetic stimulation and imaging can be used together in a multitude of ways. They can be combined together in the same sessions, or used in alternate sessions. The first three subsections below describe approaches in which TMS is combined with different imaging modalities simultaneously. These studies are frequently used to examine patterns of connectivity between brain areas. In the final subsection, we discuss studies that use both TMS and imaging, but in different sessions. Such methods can be effective tools for examining changes in connectivity patterns induced by TMS.

TMS AND POSITRON EMISSION TOMOGRAPHY

The ability to examine interregional connectivity using simultaneous TMS and positron emission tomography (PET) was first demonstrated by two studies published in 1997 (Fox et al., 1997; Paus et al., 1997). Fox et al. (1997) stimulated M1 with TMS and reported that changes in blood flow in the stimulated region were positively correlated with changes in blood flow in ipsilateral somatosensory areas, lateral premotor cortex, and contralateral supplementary motor area (SMA), and negatively correlated with changes in blood flow in contralateral M1. Paus et al. (1997) stimulated the left frontal eye field (FEF) and detected blood flow increases in the superior parietal and medial parieto-occipital regions; level of propagated activation correlated with number of TMS pulses delivered. Patterns of distal effects in both studies conformed to expectations based on connectivity studies in non-human species, providing evidence that activity in the stimulated area was propagating to those distal areas via neural connections. Soon afterward, a study examining regional cerebral glucose consumption across the brain during rTMS of the left sensorimotor cortex was published (Siebner et al., 1998). A significant increase in glucose consumption in the SMA was identified during the repetitive stimulation of sensorimotor cortex, providing evidence of neural interaction between the two regions. A later PET study by Paus et al. (2001a) showed that repetitive rTMS delivered to the left mid-dorsolateral frontal cortex robustly modulated brain activity in a fronto-cingulate circuit, which was predicted by a parallel rat experiment using electrical stimulation and field-potential recordings. More recently, TMS of prefrontal and motor cortical areas was shown to activate subcortical regions via trans-synaptic connections using simultaneous PET (Ferrarelli et al., 2004).

In addition to measuring the net neural activity in different brain regions, PET can be used to measure the activity associated with specific neurotransmitter systems. This feature of PET is particularly exciting from a neuropsychiatric perspective, as it allows researchers to probe how specific neurotransmitter systems may be disrupted in different disorders, and thus how drugs that target particular neurotransmitters may influence the function of brain networks. Combined TMS–PET studies have reported changes in dopamine and serotonin activity in regions that are distal to the stimulation site (Strafella et al., 2001, 2005; Sibon et al., 2007; Ko et al., 2008; Cho and Strafella, 2009). For example, an [11C]raclopride study of dopamine activity following stimulation of the left dorsolateral prefrontal cortex reported changes in binding in the left dorsal caudate nucleus in healthy subjects (Strafella et al., 2001) and another [11C]raclopride study of dopamine activity following stimulation of left M1 reported changes in binding in the left putamen (Strafella et al., 2003). A follow-up study in patients with early Parkinson's disease and unilateral motor symptoms revealed that the TMS-induced dopamine release in the striatum following ipsilateral M1 stimulation was lower and more spatially diffuse in the symptomatic hemisphere (Strafella et al., 2005).

In addition to Parkinson's disease, simultaneous TMS–PET has been used to examine connectivity patterns in other patient groups. Chouinard et al. (2006) studied recovery of motor function following stroke, and detected complex shifts in cross-hemisphere and basal ganglia connectivity when stimulating ipsilateral and contralateral M1 using TMS. Another study compared early versus late blind subjects and sighted controls when rTMS was delivered over sensorimotor cortex. Only the early blind group showed significant activation of early visual areas during stimulation, which was significantly greater than in late blind subjects but not when compared to controls (Wittenberg et al., 2004). These data suggest that tactile information is transmitted to early visual

regions via cortico-cortical pathways in early blind subjects, possibly providing a mechanism for enhanced tactile processing in this population.

TMS AND ELECTROENCEPHALOGRAPHY

Combining TMS with electroencephalography (EEG) to characterize connectivity was first reported by Ilmoniemi et al. (1997). Ordinary EEG amplifiers are saturated by TMS pulses. However, this difficulty was overcome by using a sample-and-hold circuit that pinned the amplifier output to a constant level during the TMS pulse with amplifier recovery in just 100 μs. Using this methodology combined with signal averaging, single pulse stimulation of the left sensorimotor cortex produced a near immediate response at the stimulated site, with spread of activation to adjacent ipsilateral motor areas within 5–10 ms and to homologous regions in the opposite hemisphere within 20 ms. Similar activation patterns were generated by magnetic stimulation of the visual cortex. A variety of other systems have since been described for simultaneous EEG/TMS recording (Thut et al., 2003; Bonato et al., 2006), and analysis approaches have been introduced for minimizing artifacts (Litvak et al., 2007).

The effects of TMS on the EEG signal have been studied both in the time domain (Paus et al., 2001b; Iramina et al., 2002; Iwahashi et al., 2008; Lioumis et al., 2009; Casali et al., 2010) and the frequency domain (Paus et al., 2001b; Iramina et al., 2002; Fuggetta et al., 2005, 2008). Several studies have reported changes in coherence between electrodes associated with the stimulation (Fuggetta et al., 2005, 2008), suggesting a reorganization in interregional interaction associated with the stimulation.

Combined TMS–EEG has been used to examine a range of clinical conditions. A study of Alzheimer's disease patients found that TMS delivered to M1 was less effective in activating widespread regions in Alzheimer's patients compared with controls (Julkunen et al., 2008). In patients with schizophrenia, TMS delivered to a premotor area was found to be less effective at eliciting responses in the gamma range in fronto-central regions when compared to healthy controls (Ferrarelli et al., 2008). These data were interpreted as indicating deficient thalamocortical interactions in this patient group. Another study compared healthy controls and patients with schizophrenia when TMS was applied to the Cz electrode position (Levit-Binnun et al., 2010); the patient group failed to generate an early phase frontal negativity (detected in the control group ~29 ms after stimulation) and demonstrated reductions in coincident parietal positivity as well as abnormalities in subsequent peaks when compared to controls. A study of epilepsy patients and controls found that TMS-induced activation at various scalp sites elicited a late phase response in a majority of patients that was absent in healthy subjects (Valentin et al., 2008). Of interest is that this method detected abnormalities in some epilepsy patients where interictal EEG records were normal.

Electroencephalography has intrinsic limitations in terms of spatial resolution. Nonetheless the very high temporal resolution of EEG allows the possibility of detecting differential effects of brain disturbance on conduction time or frequency-specific interregional oscillations that could have wide applicability for characterizing the functional networks underlying pathological conditions.

TMS AND FUNCTIONAL MAGNETIC RESONANCE IMAGING

Functional MRI has superior spatial resolution to other functional imaging modalities and temporal resolution on a seconds timescale. Furthermore, it does not expose subjects to ionizing radiation as PET does. These features make it an extremely popular imaging technique. However there are daunting technical challenges inherent in combining functional magnetic resonance imaging (fMRI) and TMS related to interference between the magnetic field of the scanner and that of the stimulator, to imaging artifacts caused by the presence of even small amounts of metal in the scanner room, and to possible torquing of the TMS coil when used in the scanner field.

Despite these technical challenges, TMS and fMRI have been used together effectively by several research labs. The capability of collecting fMRI data interleaved with TMS stimulation was first demonstrated by Bohning et al. (1998). Soon after, it was reported that activity in areas distal to the stimulation site were detected using interleaved fMRI/TMS protocols, illustrating the promise of this technique for mapping patterns of connectivity between brain areas (Bohning et al., 1999; Nahas et al., 2001; Bestmann et al., 2004).

Combined fMRI/TMS has now been used to explore the functional architecture of many different brain systems, and in some cases, to identify the functional consequences of specific interregional interactions. For example, a study stimulating the FEF reported a distinctive pattern of activity changes in early visual areas: activity increased in regions representing the peripheral visual field and decreased in regions representing the central visual field (Ruff et al., 2006). Furthermore, a psychophysical experiment confirmed that FEF stimulation enhanced contrast perception in the peripheral visual field relative to central visual field. These findings suggest that the FEF exerts top–down effects on early visual cortex in a manner that enhances contrast of peripheral relative to central stimuli.

Most combined fMRI/TMS studies to date have examined brain systems in healthy individuals, although one exception is a study of the neural basis of the perception of phantom hand movements in an amputee patient that was found to be elicited by TMS applied to the contralateral motor cortex (Bestmann et al., 2006). In a novel experimental design, TMS trials producing phantom movements were compared to trials not producing these sensations that corresponded to the same TMS intensities. The experience of phantom movement was specifically associated with coactivation in the primary motor cortex, dorsal premotor cortex, anterior intraparietal sulcus, and caudal SMA.

At present, there is great deal of unexplored potential for clinical research using combined fMRI/TMS paradigms. However, accessibility to this technique is still limited, as not many sites have developed the technical capacity for using TMS in the MR scanner.

STUDIES USING TMS AND IMAGING IN SEPARATE SESSIONS

Studies using imaging and TMS in separate sessions have been used to study a variety of phenomena, such as the neural substrates enabling functional recovery after stroke (Lee et al., 2003; O'Shea et al., 2007; Conchou et al., 2009). For the purposes of this review, the most relevant studies have used imaging to examine changes in connectivity induced by TMS.

Protocols that examine EEG coherence before and after a session of rTMS have provided a window into the cortical reorganization induced by TMS (Jing and Takigawa, 2000; Strens et al., 2002; Oliviero et al., 2003). For example, high and low-frequency rTMS to left motor cortex induced decreasing and increasing alpha-band coherence, respectively, between the stimulated site and ipsilateral premotor cortex (Strens et al., 2002; Oliviero et al., 2003). The contrasting effects of high and low-frequency rTMS on connectivity are consistent with the opposite effects of these stimulation paradigms on motor cortical excitability.

As discussed above, PET can be used in conjunction with TMS to assess connectivity. Therefore, paradigms using combined PET–TMS before and after an rTMS session can potentially provide information regarding how the rTMS session modulates connectivity (Paus et al., 2001a). However, assessment of changes in connectivity based on differences (before and after rTMS) in the activity induced in distal sites in the combined PET–TMS sessions can become complicated when the region stimulated during the PET–TMS session has an altered response to stimulation after rTMS. In such a case, changes in activity in the distal regions could be due to differences in interregional connectivity, but they could also be due to a different amount of activation in the stimulated region propagating through an unchanged connection. Alternatively, PET on its own can be used to assess connectivity if a sufficient number of PET scans can be collected for each subject. Using this approach, effective connectivity in the motor system immediately after rTMS to M1 was shown to differ from the connectivity patterns after sham stimulation of the same region (Lee et al., 2003). The changes in connectivity were similar to those seen after stroke, suggesting rTMS could provide a reversible lesion with which to study acute plasticity in the brain following stroke.

A very promising approach for studying TMS-induced connectivity changes is the use of fMRI to assess connectivity before and after rTMS. Functional magnetic resonance imaging has recently become an extremely popular tool for assessing functional (Hampson et al., inpress) and effective (McIntosh and Gonzalez-Lima, 1994; Friston et al., 2003; Goebel et al., 2003; Marrelec et al., 2005) connectivity. To date, however, fMRI studies of functional/effective connectivity before and after rTMS have been limited. However, a recent paper using dynamic causal modeling to assess effective connectivity in the motor system before and after rTMS of contralesional M1 in stroke patients illustrates the potential of this approach (Grefkes et al., 2010). rTMS reduced transcallosal connectivity between homologous parts of M1 during motor task performance and enhanced intrinsic connectivity between M1 in the lesioned hemisphere and the SMA. These changes in connectivity were accompanied by, and possibly responsible for, an improvement in motor performance.

In addition to examining changes in connectivity changes induced by TMS, studies using TMS and connectivity mapping in separate sessions can provide other forms of information. For example, a recent diffusion tensor imaging study reported that connectivity patterns predicted TMS response in patients with post-stroke pain (Goto et al., 2008).

USING CONNECTIVITY MAPPING TO TARGET TMS STIMULATION

There is wide recognition that TMS is a powerful tool for studying and modulating connectivity in the human brain, but perhaps less awareness that connectivity mapping can be a useful tool for guiding TMS stimulation. For example, when brain areas with disrupted function are not accessible to TMS, connectivity mapping can identify connected regions to be stimulated, and the inaccessible regions may thus be influenced indirectly via propagated activity patterns. Or, if the precise locus of only one region in a network of interest is known, connectivity mapping can be used to identify other nodes of a functional network in a subject-specific manner; thus multiple targets for TMS can be identified that may prove clinically effective for disrupting a pathological process involving that network.

Both structural and functional connectivity mapping can be used to identify target sites for TMS. In a study investigating the role of the prefrontal cortex in suppressing irrelevant somatosensory information during working memory tasks, diffusion tensor imaging was used to identify regions of prefrontal cortex anatomically connected with the primary somatosensory cortex (S1) in each subject (Hannula et al., 2010). Stimulation of this specific site (but not other sites) in prefrontal cortex was then shown to suppress somatosensory evoked potentials and to facilitate working memory performance, consistent with the view that the connected prefrontal region was acting on S1 in a manner that suppressed processing of irrelevant sensory stimuli.

Functional connectivity mapping has also been used to identify target regions for TMS. An example of this is a study by our group in which TMS was used to probe the circuitry involved in auditory hallucinations of schizophrenic subjects (Hoffman et al., 2007). In each subject, three to six sites were selected for stimulation. For intermittent hallucinators, the target regions were identified by comparing brain activity during hallucinations to brain activity at rest and selecting peak areas in the resulting hallucination-related activation maps. However, a subgroup of the patients in the study had continuous hallucinations and thus no rest periods for comparison purposes. For these individuals, maps of functional connectivity to Wernicke's region were created, and peaks in those maps within classic language areas were targeted. Wernicke's area was selected as the seed region for functional connectivity maps given other studies showing activation in this region during auditory hallucinations (Shergill et al., 2000). Regions showing high functional connectivity with this seed region were then targeted with "suppressive" low-frequency TMS. rTMS positioned using these functional connectivity maps did not produce better clinical responses compared to targeting Wernicke's area itself. However, a noteworthy finding is that the level of Wernicke's seeded functional connectivity assessed relative to the right homologue of Broca's area strongly and negatively predicted the capacity of low-frequency rTMS to suppress auditory hallucinations. These data suggested that especially tight functional coupling incorporating these regions was able to override rTMS effects. Consistent with this finding is a recent fMRI study showing that right homologue of Broca's area corresponds to the most prominent site of cortical activation coincident with auditory hallucinations (Sommer et al., 2008).

FUTURE DIRECTIONS

The effects of TMS at a cellular level are not well understood, and the relationship between activity of different cell types in a region and the signals measured via PET, fMRI, or EEG are also not well understood. Efforts to bridge these gaps are needed. One approach is the development of large-scale neurobiologically realistic models. For example, a model of TMS applied to visual areas during a delayed-match-to-sample task reproduced both local and distal changes in regional cerebral blood flow associated with stimulation, and allowed investigation of the different patterns of blood flow changes associated with stimulating inhibitory versus excitatory units (Husain et al., 2002). Neurobiological models that span multiple spatial scales, from cellular to systems-level neuroscience, may be particularly enlightening for neural disorders in which certain populations of cells are hypothesized to be abnormal.

Modeling of the effective connectivity between regions is also a promising avenue for future work. One of the most exciting aspects of TMS is that brain activity in one region is directly induced and the propagation of that activity to other regions can thus provide information regarding causal interactions between areas. A study using exploratory structural equation modeling of PET/TMS data extracted a model of effective connectivity (that is, of causal interactions between brain areas) with an excellent fit to the data that was also highly consistent with known anatomical connectivity (Laird et al., 2008). This suggests that combining PET/TMS (or PET/fMRI) data with structural equation modeling is a promising approach to mapping out effective connectivity in the human brain.

From a clinical perspective, more studies are needed examining how specific interventions influence brain dynamics in patient populations. A study of the effects of l-dopa on the motor network in Parkinson's disease illustrates the potential of such approaches (Buhmann et al., 2004). Stimulation of premotor cortex decreased the excitability of ipsilateral M1 in untreated Parkinson's patients, which was the opposite effect that it had in control subjects. However, a single dose of l-dopa reversed this pattern in the patients, effectively normalizing the premotor–motor interaction in Parkinson's disease. Changes in connectivity patterns associated with long-term treatments, and their associations with symptom improvements or negative side effects, could also be informative.

SUMMARY

These studies, considered together, show how diverse neuroimaging methodologies used to characterize functional connectivity and coactivation can be usefully combined with TMS. Although methodological challenges remain, these approaches provide powerful tools for investigating the network basis of a range of brain disorders. Results to date have permitted characterization of broadly distributed disconnection and hyperconnection patterns associated with Alzheimer's disease, schizophrenia, and epilepsy, and have provided intriguing glimpses into alterations in neurocircuitry associated with clinical phenomena, such as recovery from stroke. Our expectation is that these integrated studies will permit more detailed characterizations of network dynamics and connectivity that do not rely on the cognitive or task performance that is likely to be variable across individual patients, especially in illness conditions. These methods may not only elucidate pathophysiology, but may assist in diagnosis and subtyping of illness, as well as in guiding rTMS as a treatment intervention.

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