



Review

Measuring and manipulating brain connectivity with resting state functional connectivity magnetic resonance imaging (fcMRI) and transcranial magnetic stimulation (TMS)

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ABSTRACT

Both resting state functional magnetic resonance imaging (fcMRI) and transcranial magnetic stimulation (TMS) are increasingly popular techniques that can be used to non-invasively measure brain connectivity in human subjects. TMS shows additional promise as a method to manipulate brain connectivity. In this review we discuss how these two complimentary tools can be combined to optimally study brain connectivity and manipulate distributed brain networks. Important clinical applications include using resting state fcMRI to guide target selection for TMS and using TMS to modulate pathological network interactions identified with resting state fcMRI. The combination of TMS and resting state fcMRI has the potential to accelerate the translation of both techniques into the clinical realm and promises a new approach to the diagnosis and treatment of neurological and psychiatric diseases that demonstrate network pathology.

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Introduction

It is becoming increasingly recognized that many behavioral manifestations of neurological and psychiatric disease are not solely the result of abnormality in one isolated brain region but represent alterations in brain networks and connectivity. Examples include spatial neglect with imbalance in intraparietal sulcus activity

(Corbetta et al., 2005; He et al., 2007), hemiparesis worsened by transcallosal inhibition (Carter et al., 2010; Duque et al., 2005; Grefkes et al., 2008; Murase et al., 2004), memory deficits in Alzheimer's due to distributed network pathology (Buckner et al., 2005), and depression associated with limbic hyperactivity and prefrontal hypoactivity (Mayberg, 2007; Mayberg, 2009; Padberg and George, 2009). As such, much neuroscience research has shifted from focusing on the properties of individual brain regions to the interactions and connections between regions.

Brain connectivity has been non-invasively assessed in human subjects using techniques focused on three general network

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properties: anatomical connectivity, functional connectivity, and response to perturbation/stimulation. The first of these, anatomical connectivity, has relied predominantly on diffusion tensor imaging (DTI), a technique which measures the asymmetric diffusion of water molecules along white matter fiber tracks (Assaf and Pasternak, 2008). The second network property, functional connectivity, is defined as a correlation between remote neurophysiological events in the temporal domain (Friston et al., 1993; Horwitz, 2003) and has been assessed using a wide variety of techniques including electro- and magnetoencephalography (EEG/MEG), positron emission tomography (PET), near infrared spectroscopy (NIRS), and functional magnetic resonance imaging (fMRI). Given the variety of approaches used to assess functional connectivity it is important to remember that this is a broad term with some inherent ambiguity (Horwitz, 2003; Rogers et al., 2007). Derivations of functional connectivity include effective connectivity, which uses a priori models to assume directional influence (Stephan and Friston, 2010), and Granger causality, which uses data driven methods to determine whether signals in one region can be predicted by preceding signals in another (Roebroeck et al., 2005). Finally, the third network property which has served as a basis for non-invasive assessment of human brain connectivity is the brain's response to perturbation/stimulation. This approach utilizes techniques such as transcranial magnetic stimulation (TMS), focused pulsed ultrasound (Bystritsky et al., 2011), and transcranial direct current stimulation (tDCS) which can be used alone or in combination with other modalities to measure distributed brain changes occurring as a result of focal brain manipulation.

In this review we focus on two of these techniques for assessing human brain connectivity, namely resting state functional connectivity MRI (fcMRI) and TMS. This focus is motivated by the fact that resting state fcMRI is rapidly becoming the most popular of the correlational techniques for assessing functional connectivity, TMS is the most widely used perturbation approach, and the combination of the two techniques holds great promise for addressing several important clinical issues. Individual reviews have recently been written on both resting state fcMRI (Deco et al., 2011; Fox and Raichle, 2007; van den Heuvel and Hulshoff Pol, 2010) and connectivity assessed with TMS (Hampson and Hoffman, 2010; Reithler and Peters, 2011). Therefore the focus of the current review is on the overlap between the two techniques and the ways in which they can be combined. First we review how resting state fcMRI and TMS have been used individually to measure brain connectivity, including a discussion of their limitations. Second, we highlight some important similarities and differences in connectivity measured using the two techniques. Third we discuss the promise of using connectivity including resting state fcMRI to guide TMS target selection. Finally, we review evidence that TMS can be used to manipulate connectivity and discuss the potential of TMS to correct resting state fcMRI abnormalities in neurological and psychiatric disease.

Measuring connectivity with resting state fcMRI

Resting state fcMRI examines correlations in spontaneous fluctuations in the blood oxygen level dependent (BOLD) signal (for recent reviews see Deco et al., 2011; Fox and Raichle, 2007; van den Heuvel and Hulshoff Pol, 2010). In contrast to traditional task-based fMRI studies, resting state functional connectivity (fcMRI) studies examine BOLD fluctuations in the absence of any explicit input or output, while subjects simply rest in the scanner. A consistent observation is that regions with similar functional properties, such as the left and right somatomotor cortices, exhibit coherent BOLD fluctuations even in the absence of movement under resting conditions (Biswal et al., 1995; Cordes et al., 2000; De Luca et al., 2005; Fox et al., 2006b; Lowe et al., 1998) (Fig. 1A). Similar findings have been reported in multiple other brain networks including visual,

auditory, language, default mode, and corticothalamic networks (Fox and Raichle, 2007). Anticorrelations between regions with apparent opposing functional properties have also been observed (Chang and Glover, 2009; Fox et al., 2005; Fox et al., 2009; Fransson, 2005; Greicius et al., 2003) (Fig. 2D), although some debate exists surrounding the appropriate interpretation of these findings (Anderson et al., 2011; Fox et al., 2009; Murphy et al., 2009). Spontaneous BOLD fluctuations can predict the task–response properties of brain regions (De Luca et al., 2005; Vincent et al., 2006), identify subjects' aptitude for different cognitive tasks (Baldassarre et al., 2012; Hampson et al., 2006; Koyama et al., 2011; Seeley et al., 2007; van den Heuvel et al., 2009b; Zhu et al., 2011), facilitate refinement of neuro-anatomical models (Dosenbach and Fair, 2007; Fox et al., 2006a), and account for trial-to-trial variability in behavior (Fox et al., 2007; Sadaghiani et al., 2010). Resting state fcMRI correlation patterns are very robust and can be observed under sleep (Fukunaga et al., 2006; Horowitz et al., 2009; Larson-Prior et al., 2009) and sedation (Greicius et al., 2008; Kiviniemi et al., 2003; Peltier et al., 2005; Vincent et al., 2007) allowing for comparisons across development (Dosenbach et al., 2010; Fair et al., 2007) and even species (Vincent et al., 2007).

Importantly, resting state fcMRI may enjoy several practical and theoretical advantages over task based fMRI for clinical applications, including improved signal to noise, reduced need for patient compliance, avoidance of task performance confounds, and expanded patient populations (Fox and Greicius, 2010). Leveraging these advantages, significant resting state fcMRI abnormalities have been identified across almost every major neurological and psychiatric disease (for reviews see Fox and Greicius, 2010; Greicius, 2008; Zhang and Raichle, 2010). These fcMRI abnormalities have been correlated with the severity of disease in depression (Greicius et al., 2007), schizophrenia (Bluhm et al., 2007; Vercammen et al., 2010a), neglect (Carter et al., 2010; He et al., 2007), and hemiparesis (Carter et al., 2010), and can differentiate normal controls from patients with Alzheimer's disease (Greicius et al., 2004; Li et al., 2002; Supekar et al., 2008; Wang et al., 2006) or depression (Craddock et al., 2009).

Despite its potential, there are important limitations to measuring connectivity with resting state fcMRI. First, because patients are not performing a specific task there is no clear measure of performance or mental state. Second, resting state fcMRI is purely correlational in nature, not causal, limiting the conclusions that can be drawn. Third, it is difficult to separate coincidence task-evoked modulation from true connectivity. For example if one hears a beep and sees a flash at the same time the measured correlation between the visual and auditory cortex will increase, but this does not mean the synaptic strength of the connection between the regions has changed. Finally, resting state fcMRI is purely a way to measure, not manipulate functional connectivity. As resting state fcMRI abnormalities continue to be replicated, refined, and clarified, the next step will be translating this information into practical clinical interventions. In such an effort, fcMRI can offer valuable guidance and assessment tools, but combination with methods to manipulate connectivity will be critical.

Measuring connectivity with TMS

TMS is a noninvasive technique that utilizes short, rapidly changing magnetic field pulses to induce electrical currents in underlying cortical tissue (for reviews see Hallett, 2007; Kobayashi and Pascual-Leone, 2003; Wagner et al., 2007). Single pulses can be used to briefly disrupt or excite underlying cortical tissue while repeated pulses (rTMS) at different frequencies can be used to create changes in cortical excitability that outlast the duration of the stimulation itself. Such lasting modulation of cortical excitability depends on the stimulation parameters and can resemble long-term potentiation (when rTMS is applied in higher frequency, bursting patterns, e.g. in burst of 4 stimuli at 20 Hz with inter-burst pauses of 28 s) or long-

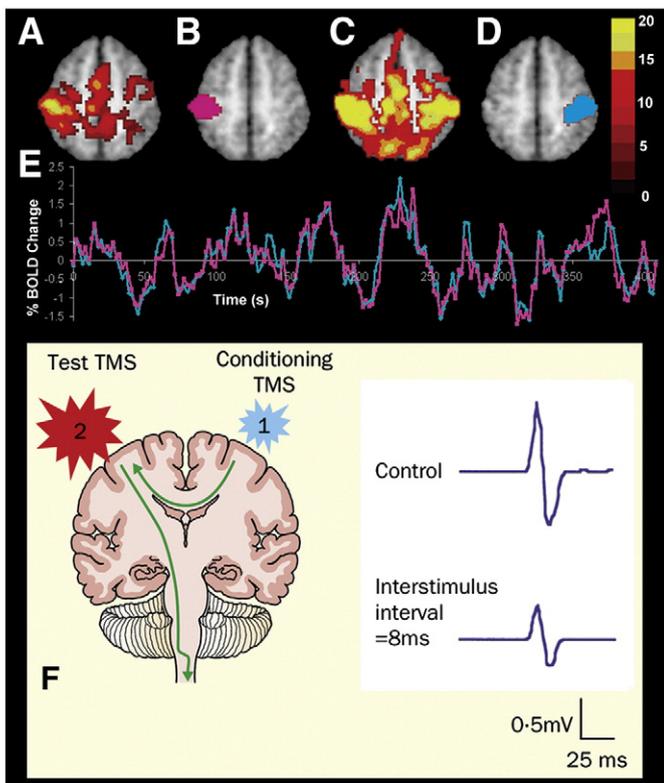


Fig. 1. Connectivity between the motor cortices assessed with resting state functional connectivity MRI and dual-coil stimulation with TMS. The top panel shows fMRI activation in response to a right hand button press (A), a left somatomotor region of interest (B), resting state functional connectivity with this left somatomotor cortex region of interest (C), a right somatomotor cortex region of interest defined on the basis of the resting state functional connectivity (D), and spontaneous fluctuations recorded in the left (pink line) and right (blue line) somatomotor cortices during the resting state conditions showing significant interhemispheric correlation (E) (modified with permission from Fox et al., 2007). The lower panel (F) shows the effect of transcallosal inhibition using dual-coil TMS. When a conditioning pulse is delivered to the left motor cortex 8 ms before the test pulse is delivered to the right motor cortex the motor evoked potential recorded from the left hand is significantly decreased (modified with permission from Kobayashi and Pascual-Leone, 2003).

term depression (when rTMS is applied at lower frequency as a continuous train, e.g. 20 min of continuous 1 Hz rTMS). The duration of these changes varies depending on the duration of the rTMS train, and can be extended to 90 min of modulation after only a few minutes of stimulation with special stimulation protocols, such as theta-burst stimulation (triplets of stimuli at 50 Hz applied at 5 Hz frequency either continuously or intermittently (Thut and Pascual-Leone, 2010)). Such rTMS-induced modulation of cortical excitability can be done safely if published recommendations and established safety standards are followed (Rossi et al., 2009). In addition to being a powerful research tool, significant clinical effects have been observed across a wide variety of neurological and psychiatric conditions (Burt et al., 2002; Fregni and Pascual-Leone, 2007; Hallett, 2007), and Neuronetics® Neurostar TMS protocol has been approved by the US Food and Drug Administration (FDA) for the treatment of certain patients with medication-resistant depression (Padberg and George, 2009). Accumulating evidence, from human and animal studies, suggests that TMS modulates neuronal activity beyond the site of stimulation, impacting a distributed network of brain regions (Ferreri et al., 2011; Ruff et al., 2009; Siebner et al., 2009; Valero-Cabre et al., 2005; Valero-Cabre et al., 2007) and that therapeutic and behavioral effects of TMS are mediated by such distributed network effects.

Given that TMS effects can propagate beyond the site of stimulation, it has become a powerful tool for measuring brain connectivity.

A simple example of a TMS-based connectivity measure involves delivering a single TMS pulse to primary motor cortex then measuring the induced contralateral muscle contraction in the form of a motor evoked potential (MEP). Note that for the TMS pulse to reach muscle it must cross synapses in the anterior horn of the spinal cord and at the neuromuscular junction. By analyzing the time it takes the TMS pulse to travel this path one can derive central conduction time, a TMS connectivity measure with some clinical utility in spinal injury (Brunholz and Claus, 1994), multiple sclerosis (Hess et al., 1986), and amyotrophic lateral sclerosis (Floyd et al., 2009).

Connectivity between separate cortical areas can be measured with TMS by pairing stimulations together with two TMS coils, aptly referred to as dual-coil experiments. In the classic example, a conditioning pulse (usually subthreshold) is applied to the primary motor cortex of one hemisphere followed by a test pulse to the motor cortex of the opposite hemisphere (Fig. 1F). If the MEP induced by the test stimulus changes with the addition of the conditioning stimulus this suggests a functional connection between the two sites. Both cortico-cortical inhibition and facilitation can be observed between motor cortices depending on the relative timing of the conditioning and test stimulus (Ferbart et al., 1992; Hanajima et al., 2001). Similar effects on primary motor cortex have been observed with conditioning pulses to cerebellar and frontal sites (Civardi et al., 2001; Ugawa et al., 1991). Dual coil experiments can also be used to assess connectivity with primary and extrastriate visual cortex, where a single TMS pulse can induce the perception of a brief flash of light, called a phosphene. Phosphene perception can be altered based on precisely timed conditioning pulses to other visual areas, frontal eye fields, or parietal cortex (Pascual-Leone and Walsh, 2001; Silvanto et al., 2006; Silvanto et al., 2009). Properly employed, dual-coil methods can be a powerful technique for probing the timing and directionality of the connectivity between cortical regions (Pascual-Leone and Walsh, 2001; Silvanto et al., 2005).

Rather than using two TMS coils, brain connectivity can also be assessed by combining TMS with a second methodology to measure remote effects of stimulation in connected brain regions. This approach has resulted in an increasing number of TMS-EEG, TMS-PET, and TMS-fMRI experiments (Bestmann et al., 2008; Hampson and Hoffman, 2010; Reithler and Peters, 2011; Ruff et al., 2009). Remote effects can be measured simultaneously with TMS in an online approach, or before and after rTMS in an offline approach. While a full review of this extensive literature is beyond the scope of this paper, we highlight a few examples to illustrate the strengths of various multi-modal TMS-based connectivity approaches. For example, the temporal resolution of EEG has been utilized to time the spread of excitation to connected brain regions following focal TMS to the primary sensorimotor cortex (Ilmoniemi et al., 1997). The spatial resolution of PET has been used to show remote cerebral blood flow (CBF) increases in the parietal/occipital cortex in response to frontal eye field stimulation (Paus et al., 1997) and remote CBF decreases in the peri-cingulate region in response to stimulation to the dorsolateral prefrontal cortex (DLPFC) (Paus et al., 2001) (Fig. 2A). Using PET radioligands specific to neurotransmitter binding sites, excitatory TMS to the left (but not right) DLPFC has been shown to cause dopamine release in the subgenual cingulate cortex (Cho and Strafella, 2009) (Fig. 2C).

Further improving on spatial resolution with fMRI, inhibitory TMS to the left dorsal premotor cortex has been shown to reduce activation in the left premotor cortex, but increase activation in the right dorsal premotor cortex and medial motor areas when subjects perform a subsequent motor task, resembling adaptive changes observed post stroke (O'Shea et al., 2007). While technically challenging, simultaneous TMS-fMRI can provide both good spatial and temporal resolution (Bestmann et al., 2008). For example, one

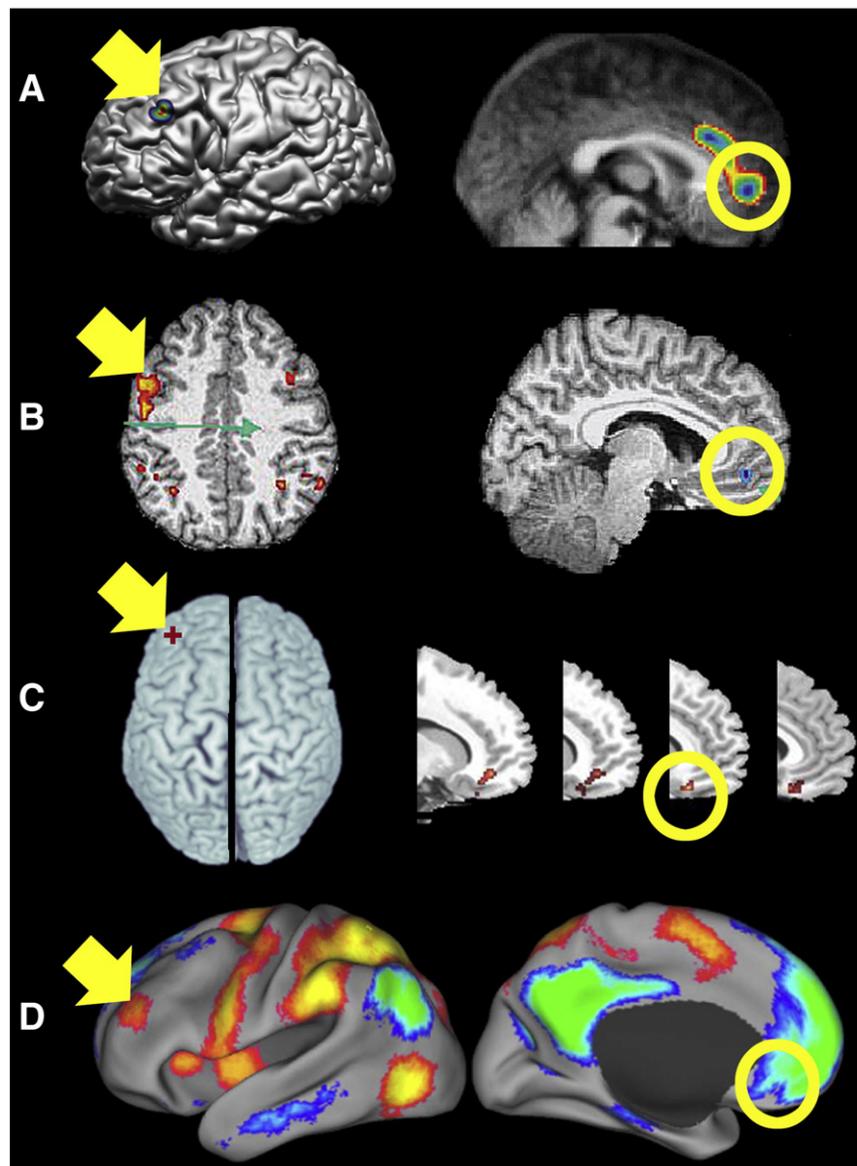


Fig. 2. Functional connectivity between the left dorsal lateral prefrontal cortex (DLPFC, yellow arrows) and ventral medial prefrontal cortex (yellow circles) assessed with TMS/Imaging and resting state functional connectivity MRI. A) Regional CBF changes assessed with PET in response to double-pulse TMS to the left DLPFC (modified with permission from Paus et al., 2001). B) BOLD changes assessed with fMRI in response to 1 Hz TMS to the left DLPFC (modified with permission from Li et al., 2004). C) Dopamine release (decreases in [11C]FLB 457 binding potential) in response to 10 Hz TMS to the left DLPFC (modified with permission from Cho and Strafella, 2009). D) Anticorrelated networks identified using resting state functional connectivity MRI based on correlations within a system and negative correlations between systems (modified with permission from Fox et al., 2005).

can examine both the distributed activation pattern and time-course of TMS to the left DLPFC (Li et al., 2004) (Fig. 2B). Using this simultaneous approach, TMS to the frontal eye fields has been shown to increase activity in retinotopic representations of the peripheral visual field, but decrease activity in the central field, a result that matches psychophysical changes in contrast perception (Ruff, Blankenburg, et al., 2006).

There are several important limitations to connectivity assessed with TMS. First, it stimulates neuronal tissue exogenously and artificially, thus connectivity revealed by TMS may be different than connectivity present under more physiological conditions. Second, TMS can only selectively target areas along the cortical surface, thus assessing connectivity to or between deep brain structures becomes difficult or impossible. Presently available ‘deep TMS coils’ such as the H-coil can enable penetration to deeper brain structures, but also stimulate surface cortex immediately under the coil and thus do not allow for selective deep stimulation (Deng and

Peterchev, 2008; Roth et al., 2007). Eventually, multi-coil TMS arrays may offer technical solutions to this limitation. Third, connectivity measured with TMS alone (e.g. dual coil paradigms) can only be assessed in cortex with a clear TMS output effect (e.g. motor or visual cortices) and connectivity between other structures necessitates the addition of a secondary monitoring method (e.g. EEG or neuroimaging). Fourth, remote changes observed in response to TMS with EEG or neuroimaging could reflect other factors besides propagation of TMS activity along cortical connections creating some interpretive ambiguity. These factors could include associated effects of TMS (e.g. tapping sensation or clicking noise), behavioral or cognitive consequences of the TMS leading to changes in brain activity, or neuronal adaptation to the TMS perturbation. Finally, the selection of an appropriate stimulation target is an ongoing clinical problem in TMS, an issue that will be discussed further in our section on using functional connectivity to guide TMS target selection.

Does connectivity measured with fMRI and TMS reflect the same underlying phenomenon?

TMS and resting state fMRI are complimentary techniques that if combined might compensate for the limitations of either technique alone, providing insight into a variety of neuroscience questions and facilitating the translation of both techniques into clinical care. A first step towards combining these techniques is to determine if connectivity assessed with resting state fMRI is the same as connectivity assessed with TMS. Unfortunately, there have been no experiments that directly compare the two connectivity measures in the same subjects. However, by comparing results across different studies some useful insights can be gained.

As one might expect, connectivity assessed using either resting state fMRI or TMS is related to and constrained by underlying anatomical connectivity. DTI, a noninvasive measure of anatomical connectivity, has been shown to relate well to both functional connectivity measured with resting state fMRI (De Luca et al., 2006; Greicius et al., 2009; Honey et al., 2009; Koch et al., 2002; Lowe et al., 2008; Skudlarski et al., 2008; van den Heuvel et al., 2008; van den Heuvel et al., 2009a; Zhang et al., 2010) and connectivity as assessed with TMS (Voineskos et al., 2010; Wahl et al., 2007). Some of the strongest evidence comes from studies relating individual differences in transcallosal connectivity measured with DTI to that measured with resting state fMRI (Lowe et al., 2008), paired pulse TMS (Wahl et al., 2007; Wahl et al., 2011), and TMS–EEG (Voineskos et al., 2010). Surgical sectioning of the corpus callosum disrupts inter-hemispheric connectivity assessed with resting state fMRI (Johnston et al., 2008) and individuals with agenesis of the anterior trunk of the corpus callosum show disrupted transcallosal inhibition with paired pulse TMS (Meyer et al., 1995). It is important to note that connectivity assessed with either technique involves polysynaptic connections. For example, resting state fMRI is present between regions in the monkey visual system with no direct anatomical connections (Vincent et al., 2007), and the simple presence of a muscle twitch after TMS to the motor cortex implies polysynaptic transmission.

An advantage of both fMRI and TMS over purely anatomical connectivity measures is that they can provide information on the functional consequences of anatomical connections. Both resting state fMRI and TMS have revealed results potentially consistent with excitatory versus inhibitory connections, however interpretation of these results and the relationship between techniques is likely to be complicated. For example, the bilateral somatomotor cortices are positively correlated when connectivity is assessed with resting state fMRI (Fig. 1A). This is consistent with inter-hemispheric facilitation using dual-coil TMS (Hanajima et al., 2001), changes in motor cortex excitability matching excitatory/inhibitory rTMS to the opposite side (Gorsler et al., 2003), and some TMS–PET findings showing a contralateral increase in activity in response to excitatory M1 stimulation (Ferrarelli et al., 2004; Siebner et al., 2000). However dual-coil TMS can also produce transcallosal inhibition (Ferbert et al., 1992) (Fig. 1B) and other TMS–PET studies have reported contralateral decreases in motor cortex activity in response to ipsilateral stimulation (Fox et al., 1997; Fox et al., 2006c).

In a second example of how these techniques may provide insight into the functional consequences of anatomical connections, we consider the relationship between the left dorsal lateral prefrontal cortex (DLPFC) and the ventral medial prefrontal cortex (Fig. 2). TMS–fMRI (Li et al., 2004), TMS–PET measuring CBF (George et al., 1999; Paus et al., 2001), TMS–PET measuring dopamine binding (Cho and Strafella, 2009), and resting state fMRI (Fox et al., 2005) all suggest a functional connection between these two regions (Fig. 2) which may have precedence in track tracing results in monkeys (Petrides and Pandya, 1999; Vogt and Pandya, 1987). Interestingly, TMS–fMRI (Li et al., 2004), TMS–PET measuring CBF (George et al., 1999; Paus et al., 2001), and resting state fMRI (Fox et al., 2005) all

suggest that this interaction may be inhibitory, such that when the DLPFC is stimulated with TMS or activity in the DLPFC increases spontaneously, activity in the ventral medial prefrontal cortex is suppressed. Obviously there is significant heterogeneity in the DLPFC and combined studies are needed before any real conclusions can be drawn, however this convergence across techniques could have important implications for network models of depression (Mayberg, 2007). Further, there has been substantial debate surrounding the interpretation of anticorrelations observed with resting state fMRI (Anderson et al., 2011; Fox et al., 2009; Murphy et al., 2009), and evidence showing that stimulation to one region could causally suppress activity in an anticorrelated region would go far in validating the functional importance of this relationship.

An important area where the relationship between resting state fMRI and TMS is unclear is in context dependence of the measured connectivity. The idea that neuronal networks reorganize in the context of different task conditions has a strong precedent (Marder and Weimann, 1991), and animal studies have shown context-dependent changes in neuronal synchrony (Engel et al., 2001; Varela et al., 2001). Similarly, accumulating evidence suggests that connectivity assessed with TMS depends on the task context (Koch and Rothwell, 2009; Ruff et al., 2009). For example, in an elegant dual-coil TMS study connectivity was assessed between the left dorsal premotor cortex (conditioning pulse) and right primary motor cortex (test pulse) during a task in which subjects were cued to move either their right or left hand (Koch et al., 2006). A facilitatory connection was observed 75 ms after a tone indicating left hand movement (but not right hand movement), while an inhibitory connection was observed 100 ms after a tone indicating right hand movement (but not left hand movement). This shows that the strength and sign of the functional connection between these two regions varies with both time and task context.

Due to its poorer temporal resolution and inability to exert causal perturbations, the context dependence of connectivity assessed with fMRI remains less clear. Many groups have reported changes in fMRI between rest conditions and task performance (Arfanakis et al., 2000; Bartels and Zeki, 2005; Cordes, et al., 2000; Fransson, 2006; Hampson et al., 2002; Hampson et al., 2004; Jiang et al., 2004; Lowe et al., 2000; Morgan and Price, 2004; Nir et al., 2006; Sun et al., 2006), generally reporting an increase in the correlation between regions similarly activated by the task and a decrease between regions not similarly activated. However, interpretation of these results is confounded by the superposition of task-evoked activity on top of resting state fluctuations (Fox et al., 2006b) and apparent context-dependent changes in connectivity can disappear after correction for task-evoked activity (Arfanakis et al., 2000). Examining resting state fMRI before and after tasks can circumvent this confound, an approach that has been used to document modulation of resting state functional connectivity by learning tasks (Albert et al., 2009; Lewis et al., 2009; Tambini et al., 2010).

Finally, both techniques have identified connectivity changes across a range of altered states including neurological and psychiatric conditions with both concordant and discordant results (Burt et al., 2002; Fox and Greicius, 2010; Fregni and Pascual-Leone, 2007; Greicius, 2008; Hallett, 2007; Zhang et al., 2010). For example, both measures agree that there is a decrease in connectivity with sleep (Horovitz et al., 2009; Massimini et al., 2005), sedation (Ferrarelli et al., 2010; Greicius et al., 2008), and across the corpus callosum in patients with multiple sclerosis (Lowe et al., 2008; Wahl et al., 2011). However in blind subjects TMS–PET suggests increased connectivity between primary somatosensory and visual cortices (Wittenberg et al., 2004) while resting state fMRI suggests that connectivity is decreased (Liu et al., 2007; Yu et al., 2008). Further work combining both measures in the same subjects and patient populations is needed to help understand the similarities and differences in these two connectivity techniques.

Using connectivity to guide TMS

The recognition that one is manipulating a network and not just a single brain region with TMS complicates an ongoing difficulty: How does one select the optimal site for stimulation? For example, clinical TMS for treatment of depression identifies the dorsal-lateral prefrontal cortex (DLPFC) stimulation site by moving 5 cm anterior to the motor cortex (George et al., 1996; Pascual-Leone et al., 1996), a technique which frequently misses the DLPFC completely (Ahdab and Ayache, 2010; Herwig et al., 2001) and contributes to variability in clinical response (Herbsman et al., 2009; Padberg and George, 2009). TMS effects can be improved by targeting based on individual MRI anatomy (Fitzgerald et al., 2009; Gugino et al., 2001) and even further augmented using individual fMRI derived activation foci (Sack et al., 2009). However, these approaches have translated into only modest clinical improvements. For example, anatomical DLPFC targeting improved depression scores more than standard targeting, but the study's primary outcome measure failed to reach significance (Fitzgerald et al., 2009). Similarly, three depression trials targeting TMS based on foci of hypometabolism in the prefrontal cortex failed to improve patient outcomes beyond standard targeting (Garcia-Toro et al., 2006; Herwig et al., 2003; Paillère Martinot et al., 2010). One of the critical limitations of these efforts to improve TMS targeting may be that they have focused on the stimulation site alone and have not taken into account the distributed network properties of the targeted region.

Despite its potential, surprisingly few studies have used distributed network connectivity to guide TMS target selection. In an excellent example of how connectivity can guide TMS, diffusion tensor imaging (DTI) was used to identify subject-specific targets in the middle frontal gyrus that were connected to a particular portion of primary somatosensory cortex (Hannula et al., 2010). TMS to this focus improved tactile working memory, but not TMS to non-connected portions of the middle frontal gyrus located just 18 mm away.

A few studies have used task-based fMRI measures (as opposed to resting state fMRI) to identify stimulation targets (Bien and Roebroek, 2009; de Graaf et al., 2009; Zanto et al., 2011). In perhaps the best example of this approach, functional connectivity with extrastriate visual areas (V4 and V5) during the encoding phase of a

selective-attention delayed-recognition task was used to identify subject-specific targets in the inferior frontal junction (IFJ) thought to be involved in top-down modulation (Zanto et al., 2011). Inhibitory TMS to this site disrupted both behavioral performance and EEG measures of top-down influence. Further, the magnitude of the TMS-induced change in EEG was related to the strength of functional connectivity between IFJ and V4 across subjects. Similar studies have used task-based functional connectivity to target frontal TMS targets correlated with posterior parietal cortex during a visuospatial judgment task (de Graaf et al., 2009) or correlated with regions involved in a set of imitation tasks (Bien and Roebroek, 2009) with similar disruption in task performance. Although these studies certainly speak to the potential of functional connectivity to guide TMS target selection, an issue that complicates interpretation of these findings is the fact that the frontal targets are themselves activated by the task. It is therefore difficult to determine if it is truly the connectivity to other regions that mediates the frontal TMS effect, or if these regions could be identified just as well using traditional activation mapping. If the latter is true, the observed TMS effect could simply be the result of disrupting another region involved in the task without any clear dependence on connectivity. Further efforts linking the magnitude of TMS-induced changes to the strength of the functional connectivity between regions (Zanto et al., 2011), or showing that TMS to a connected region not modulated by the task has an effect on task performance will be important in clarifying these issues.

Finally, a handful of studies have begun using resting state fMRI to guide TMS target selection. Eldaief and colleagues recently used resting state fMRI with the posterior cingulate to target rTMS to a connected region of the lateral parietal cortex in order to modulate activity within the default mode network (Eldaief et al., 2011). In an early example of using resting state fMRI to guide therapeutic TMS, Hampson and colleagues targeted inhibitory TMS to regions correlated with Wernikes area in a small set of patients with schizophrenia and continuous auditory hallucinations (Hoffman et al., 2007). Unfortunately rTMS to these targets did not lead to symptomatic improvement. Recently, we have examined the utility of resting state fMRI to address the above referenced clinical problem of determining where to target rTMS in the DLPFC to improve antidepressant response (Fox et al., 2012). We first identified DLPFC

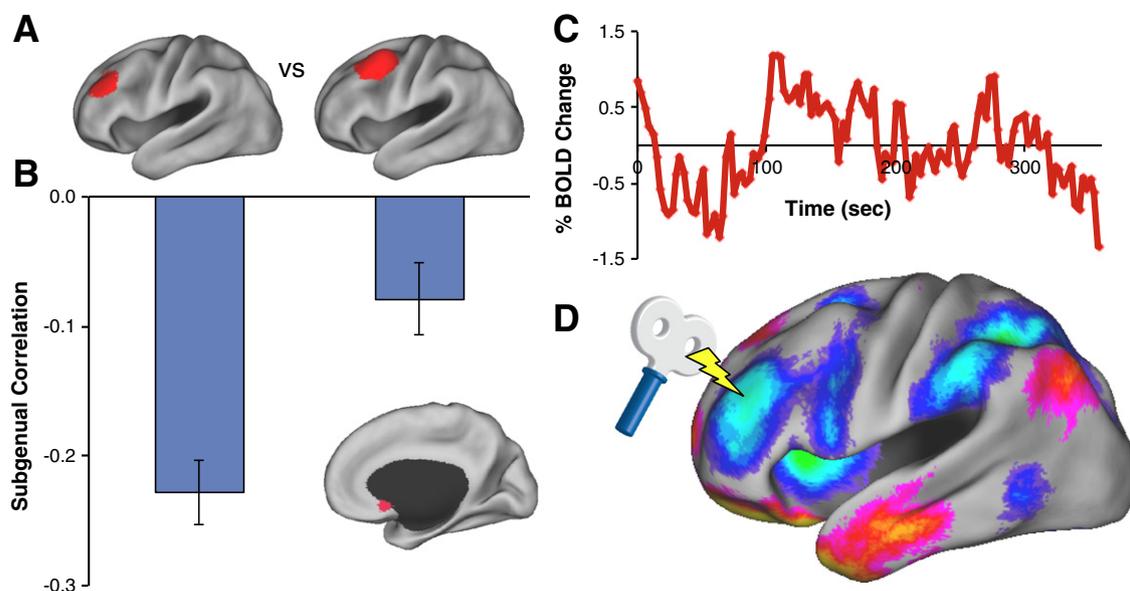


Fig. 3. Using resting state fMRI to target therapeutic TMS. A) TMS targets in the left dorsal lateral prefrontal cortex (DLPFC) known to be more effective (left) versus less effective (right) at producing an antidepressant response. B) Resting state functional connectivity reveals that the more effective target is more negatively correlated (anticorrelated) with the subgenual (inset) compared to the less effective target. C) Resting state BOLD time course extracted from the subgenual. D) Resting state functional connectivity identifies a theoretically optimal stimulation target in the left DLPFC based on anticorrelation with the subgenual. (Modified from Fox et al., 2012).

target coordinates known to be more effective versus less effective based on prior TMS clinical studies (Fitzgerald et al., 2009) (Fig. 3A). We then examined differences in fMRI between these two targets and found that more effective sites were more negatively correlated (anticorrelated) with the subgenual cingulate cortex, a region thought to play a key role in the pathophysiology of depression and antidepressant response (Drevets et al., 2008; Mayberg, 2009; Mayberg et al., 2005) (Fig. 3B). Based on these results, we extracted the BOLD time course from the subgenual cingulate (Fig. 3C) then used fMRI to identify a theoretically optimal target site in the DLPFC (Fig. 3D). While this initial analysis was performed on a population of subjects, this approach could be similarly used to identify individualized TMS targets for specific patients. Obviously, clinical trials are needed to determine the clinical utility of this approach, but this connectivity-based targeting paradigm has the potential to improve therapeutic stimulation across a range of diseases with distributed network pathology.

Moving forward, we anticipate great value in targeting TMS based on individualized connectivity with distributed brain networks, however there are a number of obstacles which must be overcome to validate the clinical utility of such a targeting approach. We delineate these obstacles here to encourage initiatives in this regard:

- 1) Identification of a remote region or network to be manipulated
- 2) Connection between the region or network one is trying to manipulate and a target on the cortical surface accessible by TMS

- 3) Spatial heterogeneity of the connectivity in the targeted region (for targeting based on connectivity to be advantageous to anatomy alone)
- 4) Subject to subject heterogeneity of the connectivity of the targeted region (for individualized targeting to be advantageous over average coordinates)
- 5) Reproducibility of individualized target identification across sessions

Manipulating connectivity with TMS

A unique advantage of TMS compared to fMRI, and every other noninvasive approach for assessing connectivity, is that TMS can also be used to manipulate connectivity. In fact, it is becoming apparent that some of the clinical effects of rTMS may be due more to TMS induced changes in connectivity between brain regions than local effects on the stimulated region itself (Grefkes et al., 2010). Further, as techniques such as resting state fMRI continue to identify reproducible pathological abnormalities in connectivity the ability of TMS to manipulate connectivity will become increasingly important.

Two different TMS-based approaches have been employed to alter connectivity, repetitive TMS (rTMS), by far the most popular approach, and paired associative stimulation (PAS), which will be discussed later. While it can be argued that the local effects of rTMS on cortical excitability are due to changes in connectivity within the

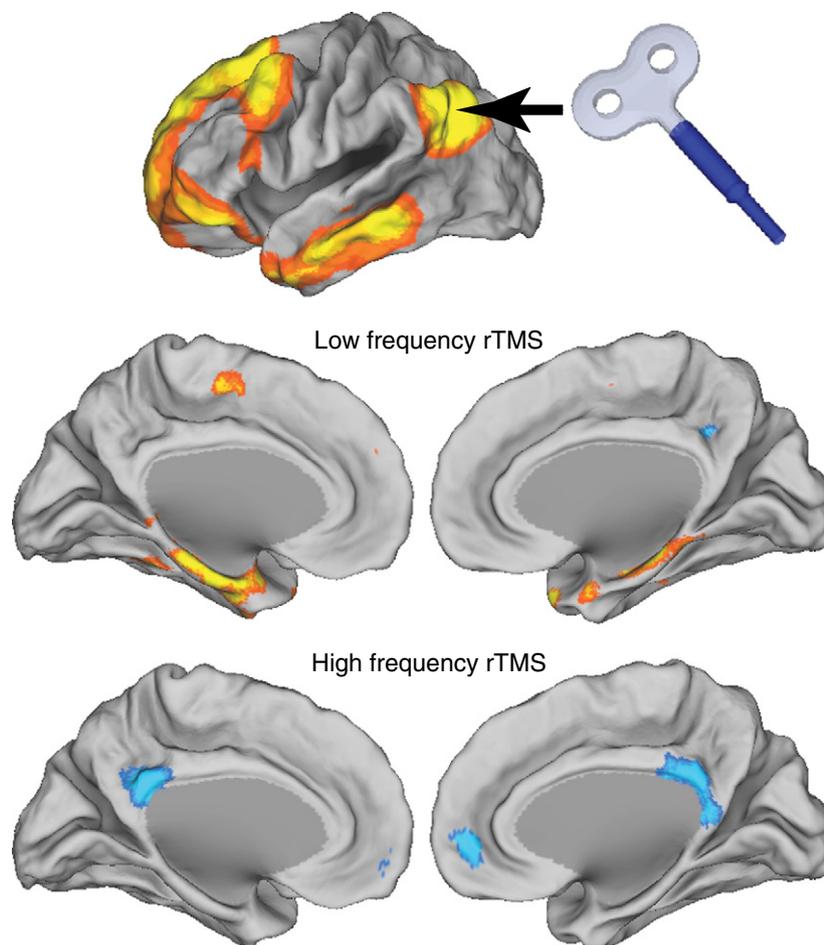


Fig. 4. Modulating resting state functional connectivity networks using TMS. Both inhibitory and excitatory TMS were applied to the left inferior parietal lobule, part of the default mode network (top row). Inhibitory TMS resulted in pronounced increases in functional connectivity between the stimulation site and the medial temporal lobe (middle row) while excitatory TMS resulted in decreased correlation between the stimulation site and other nodes of the default mode network (bottom row). (Modified from Eldaief et al., 2011).

stimulated region itself, the current review is focused on connectivity between brain regions. rTMS induced changes in connectivity between regions have been studied using a wide variety of connectivity measurement techniques including dual-coil TMS (Pal et al., 2005), TMS–PET (Paus et al., 2001), EEG coherence (Fuggetta et al., 2008; Jing and Takigawa, 2000; Oliviero et al., 2003; Strens et al., 2002; Zanto et al., 2011), task-based effective connectivity with PET (Lee et al., 2003), task-based effective connectivity with fMRI (Grefkes et al., 2010; Pleger et al., 2006), and finally resting state fcMRI (Eldaief et al., 2011; van der Werf et al., 2010; Vercammen et al., 2010b) (Table 1).

Given the variety of different connectivity measurement techniques used in the above studies, it is highly likely that rTMS can indeed be used to alter cortico–cortical connectivity. Each of these different approaches offers unique advantages and disadvantages; however taken collectively they raise several important points regarding assessing rTMS-induced connectivity changes.

First, it is important to consider whether an observed change in connectivity actually reflects a change in connection strength between remote areas or whether it could be explained by local effects of the rTMS alone. This is particularly problematic if TMS perturbation to the area just stimulated with rTMS is part of the connectivity measure (Paus et al., 2001; Pal et al., 2005). Pal et al. showed appropriate concern for this issue in their dual-coil paradigm by adjusting the conditioning stimulus to maintain motor evoked potential amplitude; however this cannot completely exclude local effects not measured by the MEP. Even if one is not using TMS as part of the connectivity measure, differentiating changes in connectivity from purely local effects remains difficult. Studies that find a change in connectivity between remote regions that have not been stimulated make an important advance in this regard (Davare et al., 2010; Grefkes et al., 2010; van der Werf et al., 2010). Second, when connectivity is being assessed during a task, it is important to determine if the measured change in connectivity is actually due to a change in behavior (as opposed to the change in behavior being due to a change in connectivity). Studies in which the stimulation does not change task performance are helpful in excluding this possibility (Lee et al., 2003), but note that a change in cognitive or behavioral strategy could alter brain activity while not being captured by task performance. Third, it is important to control for as many non-specific effects as possible. An ideal study would vary stimulation frequency, stimulation site, and the networks examined to show maximal specificity of an rTMS induced connectivity change. For example, excitatory rTMS over primary motor cortex decreased ipsilateral cortico–cortical alpha band coherence (Oliviero et al., 2003) while inhibitory stimulation increased it (Strens et al., 2002), showing specificity of the observed connectivity change for the stimulation frequency. Finally, in the case of effective connectivity it is important to recognize that results will be constrained by the model applied. Other regions or connections not included in the model could be significantly altered and would be missed by the model-driven analysis.

Assessing rTMS induced connectivity changes with resting state fcMRI may help avoid some of the above interpretive difficulties; therefore we expect studies in this area to increase. An early study to examine such effects acquired resting state fcMRI data following low frequency rTMS to left DLPFC and sham stimulation (van der Werf et al., 2010). In an analysis restricted to the default mode network, they showed that rTMS resulted in a reduction in functional connectivity between the default mode network and lateral temporal cortices with a trend towards reduced functional connectivity with the bilateral hippocampus. Although sham controlled, they did not show specificity of the effect to their network of interest, stimulation site, or stimulation frequency. A recent study incorporating some of these additional controls acquired resting state fcMRI data before and after low and high frequency stimulation to the left posterior inferior parietal lobule, a node of the default mode network (Eldaief et al., 2011). Following low frequency rTMS, intrinsic correlations

were increased between the stimulation site and the hippocampal formation. Following high frequency stimulation, correlations between multiple nodes of the default mode network were decreased but correlations with the hippocampus were unchanged (Fig. 4). No significant effects were seen in other networks such as somatomotor, visual, or auditory. While this study was again limited to one stimulation site, they showed specificity for their network of interest and stimulation frequency. Comparing results across these two rTMS–resting state fcMRI studies, low frequency stimulation appears to have opposite effects on functional connectivity between the default mode network and the hippocampus depending on the stimulation site. Interestingly, resting state fcMRI correlations observed between the two stimulation sites and the hippocampus are also opposite; the DLPFC is negatively correlated with the hippocampus while the inferior parietal lobule is positively correlated (Fig. 2D) (Fox et al., 2005). Whether this observation is anything more than coincidence will require future work.

The ability of rTMS to manipulate connectivity as measured by resting state fcMRI raises the possibility that it may be used to modify resting state fcMRI abnormalities observed in disease states that might result in behavioral gains for the patient. The above rTMS-induced manipulations of resting state fcMRI in the default mode network may prove valuable in disorders where fcMRI abnormalities in this network have been observed, including schizophrenia (Whitfield-Gabrieli et al., 2009), depression (Greicius et al., 2007) and Alzheimer's disease (Greicius et al., 2004). To our knowledge, only one study of rTMS-induced changes in connectivity has been aimed at rectifying resting state fcMRI abnormalities in patients (Vercammen et al., 2010b). Based on prior work relating the severity of auditory hallucinations to reduced resting state connectivity between the left temporal parietal junction (TPJ) and bilateral cingulate and amygdala (Vercammen et al., 2010a) and evidence that inhibitory rTMS to the left TPJ could improve these symptoms (Freitas et al., 2009), it was hypothesized that rTMS might normalize functional connectivity between these regions. In a study of 18 patients with schizophrenia there was a trend towards symptomatic benefit but no rTMS-induced change in resting state connectivity between the left TPJ and bilateral cingulate or amygdala (Vercammen et al., 2010b). However there was an rTMS-induced increase in connectivity between the left TPG and right insula not seen with sham stimulation.

The above study in patients with auditory hallucinations represents an excellent example of how one might combine resting state fcMRI with TMS to identify then correct abnormalities in brain connectivity, however, it is important to realize that in the pathological brain, restoring a normal pattern of activity within a given neural network may not be the most effective way to suppress symptoms. Instead, what might need to be done is induce other changes that may prove behaviorally more adaptive. In addition, the study by Vercammen et al. (2010b) also highlights a potentially important limitation of rTMS. While rTMS does appear to alter connectivity, it currently seems to do so in unpredictable ways, often between unexpected regions. If the goal is to selectively increase or decrease connectivity between specific brain regions in a controlled manner, advances in our understanding of rTMS or alternative approaches will likely be needed. One alternative approach that may help address this issue is termed paired associative stimulation and uses Hebbian principles of synaptic plasticity to modify connectivity in a highly controlled manner.

The original studies of paired associative stimulation dealt not with cortical–cortical connections, but connections between cortex and peripheral nerve (Stefan et al., 2000; Wolters et al., 2003). If stimuli to the median nerve and motor cortex are paired with an ISI of 25 ms (such that they arrive nearly simultaneously at the motor cortex) a phenomenon similar to long-term potentiation occurs. A subsequent TMS pulse to the motor cortex will result in a larger motor

Table 1
Connectivity changes in the human brain observed in response to focal rTMS.

Connectivity measurement	Stimulation	Connectivity change	Comments	References
Dual-coil TMS during rest	Inhibitory rTMS to primary motor cortex	Decreased inter-hemispheric inhibition with contralateral M1	Difficult to exclude local effects (although persists when the strength of the conditioning stimulus is adjusted)	Pal et al. (2005)
Dual-coil TMS during rest and task	Inhibitory rTMS (continuous theta burst) to the anterior intraparietal area	Decreased connectivity between ventral premotor and M1 during grasp preparation	Effects were context dependent (not seen during rest)	Davare et al. (2010)
Resting state EEG coherence	Excitatory rTMS to primary motor cortex	Decreased ipsilateral cortico–cortical alpha band coherence		(Fuggetta et al., 2008; Oliviero et al., 2003)
Resting state EEG coherence	Inhibitory rTMS to primary motor cortex	Increased ipsilateral cortico–cortical alpha band coherence	Effects observed up to 25 min post stimulation	Strens et al. (2002)
Resting state EEG coherence	Excitatory rTMS to the left frontal area	Increased directed coherence from stimulated site to other cortical nodes (especially parietal)	Intra-hemispheric change more pronounced than the inter-hemispheric change	Jing and Takigawa (2000)
Task-based EEG coherence	Inhibitory rTMS to the premotor area	Increase in task related coherence between motor regions		Chen et al. (2003)
Task-based EEG coherence	Inhibitory rTMS to the right inferior frontal junction	Decreased ipsilateral alpha band coherence during task		Zanto et al. (2011)
Resting state TMS–PET	Excitatory rTMS to the left DLPFC	Increased connectivity from DLPFC to cingulate regions	Difficult to exclude local effect of rTMS on the DLPFC	Paus et al. (2001).
Resting state functional connectivity with PET	Inhibitory rTMS to the left temporal–parietal junction	Decreased connectivity between the stimulated node and a wide variety of regions	Difficult to exclude local effect of rTMS on the TPJ, performed in patients with schizophrenia and auditory hallucinations	Horacek et al. (2007)
Task-based effective connectivity with PET	Inhibitory rTMS to primary motor cortex	Decreased connectivity between stimulated M1 and premotor/mesial motor areas. Increased coupling between an inferomedial portion of M1 and anterior motor areas.		Lee et al. (2003)
Task-based effective connectivity with fMRI	Excitatory rTMS to primary sensory cortex	Increased effective connectivity from S1 to M1	Persists up to 120 min; correlated with behavioral improvement in tactile discrimination	Pleger et al. (2006)
Task-based effective connectivity with fMRI	Inhibitory rTMS to contralesional M1 in stroke patients	Increased effective connectivity between ipsilesional M1 and ipsilesional SMA	Related to clinical improvement in the movement of the paretic hand	Grefkes et al. (2010)
Resting state fcMRI	Inhibitory rTMS to the left TPJ versus sham	Increased connectivity between the left TPJ and the right insula	Performed in patients with schizophrenia and auditory hallucinations	Vercammen et al. (2010b)
Resting state fcMRI	Inhibitory rTMS to the left DLPFC versus sham stimulation	Decreased connectivity between the DMN and lateral temporal cortices; trend towards decreased connectivity with the hippocampus.		van der Werf et al. (2010)
Resting state fcMRI	Excitatory and Inhibitory rTMS to the left inferior parietal lobule	Excitatory: Decreased connectivity within the DMN Inhibitory: Increased connectivity with hippocampus		Eldaief et al. (2011)

evoked potential in median innervated muscles suggesting that the connection strength has been increased. If the ISI is changed to 10 ms (such that there is an offset of 15 ms at the motor cortex) a phenomenon similar to long-term depression occurs and subsequent MEPs will be decreased. Derivations of this technique have used endogenous motor activity rather than median nerve stimulation (Thabit et al., 2010) or timed stimuli to arrive with specific offsets in the spinal cord rather than the motor cortex (Cortes et al., 2011) with similar effects. However, the most pertinent derivation of this technique for the present discussion is the use of paired associative stimulation to specifically modulate cortico–cortical connections (Buch et al., 2011; Plewnia et al., 2008; Rizzo et al., 2009).

In the first paper to use this approach, two TMS coils were used to apply simultaneous 10 Hz stimulation to both the left primary motor cortex and the visual cortex at the occipital pole, with the goal of enhancing polysynaptic connectivity between the two regions (Plewnia et al., 2008). An increase in EEG coherence was seen specifically on the stimulated side that was not seen with M1 stimulation alone. While provocative, this study did not vary the timing of the stimuli to show specificity to simultaneous stimulation versus independent effects of rTMS at the two sites. A subsequent study applied single pulses to the left then right motor cortices at a delay of 8 ms and

frequency of 1 Hz (Rizzo et al., 2009). Following 90 of these paired pulses, but only at this specific delay, there was a marked reduction in inter-hemispheric inhibition. While solidifying the importance of timing, it remains unclear why this study resulted in a decrease rather than an increase in connectivity. Finally, in perhaps the clearest example of this approach, paired associative stimulation was used to modulate connectivity strength between the ventral premotor cortex and M1 (Buch et al., 2011). Applying pulses first to ventral premotor cortex followed by M1 at an appropriate delay led to an increase in the connection strength between these two regions. The effect was anatomically specific and reversing the order of the paired stimuli led to a reversal of the effect (i.e. a decrease in connectivity). Particularly promising for improving the duration of therapeutic TMS, residual effects on connectivity could be seen up to 3 h after the stimulation (Buch et al., 2011). Although currently limited to TMS accessible sites on the cortical surface, the technique of cortico–cortical paired associate stimulation shows great promise for selectively increasing or decreasing connectivity between specific brain regions. Future work is needed to determine if this approach can lead to behavioral manifestations and whether it will be useful for modifying connectivity abnormalities observed with resting state fcMRI in neuropsychiatric disorders in order to promote symptomatic relief.

Conclusions

TMS and resting state fMRI are complimentary approaches for assessing brain connectivity with individual limitations that might be overcome by combining the two techniques. Areas of particular value include using connectivity to guide TMS target selection and using TMS to modulate abnormal network interactions identified with resting state fMRI. Together, they may further insight into a variety of interesting neuroscience questions, facilitate the translation of both techniques into clinical care, and move us closer to the goal of a reliable, noninvasive method for controlled, individualized neural network modulation.

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