Research Protocol Summary

1. Protocol Title: Effects of rTMS on human brain activity measured with EEG and fMRI

Note: This protocol covers three studies (Aims 1-3) of a NIMH BRAIN R01 grant supporting this research currently under review.

2. Purpose of the Study:
Treating psychiatric and motor disorders without surgery or life-long pharmacology is a vexing but attainable goal. One avenue of progress has been the development of non-invasive brain stimulation methods such as repetitive transcranial magnetic stimulation (rTMS). This project investigates the effects of rTMS on neural circuits as a function of spatiotemporal parameters and brain state in order to better understand why the method works and how to improve its efficacy. Leveraging our expertise in application of TMS methodology during concurrent single neuron recording techniques in non-human primates and imaging and scalp potential techniques in humans (fMRI and EEG), we aim to resolve three interlocking problems in the design and application of rTMS: **stimulation frequency**, **spatial targeting**, and interactions with **brain state**.

Primary Objective: Investigate rTMS temporal parameters: impact of frequency (1Hz versus 5Hz versus 10Hz rTMS) and number of pulses.
Primary Endpoint: We make 2 general predictions. **(1)** 1Hz vs. 5/10Hz rTMS will have inhibitory vs. excitatory effects on behavior (reaction times—RTs) and motion-related (high vs low coherence) medial temporal (MT) activity (in both EEG, and fMRI). **(2)** Excitatory effects for 10Hz will increase with number of pulses.

Secondary Objective: Examine rTMS spatial targeting: recruitment of specific networks in either dorsal (rTMS-D) or ventral (rTMS-V) pathways.
Secondary Endpoint: We predict that compared to the control condition, rTMS-D will enhance motion task performance and motion-related (high vs. low coherence) activity in the dorsal pathway (e.g., FEF, IPS), whereas rTMS-V will enhance motion-related activity in ventral pathway, with little or no effect on motion task performance.

Tertiary Objective: Establish rTMS brain state-dependency: stimulation of active versus inactive regions.
Tertiary Endpoint: We predict that rTMS effects on MT activity will be potentiated during motion task blocks compared to both color task and rest blocks.

3. Background & Significance:
Non-invasive methods for stimulating the human brain show great promise for safe, effective treatments of psychiatric and motor disorders, and are in widespread use for basic research on human behavior and cognition. One such method, transcranial magnetic stimulation (TMS), is the application of time-varying magnetic fields above the scalp that induce transient electrical fields in the brain. TMS clearly stimulates the brain and affects behavior, but we do not know why it works; its effects on neural activity within brain regions and networks are not understood at a biological level. This project seeks to determine the neural basis of effects caused by TMS as applied in sequences of pulses, known as repetitive TMS (rTMS), a technique approved by the FDA for the

treatment of depression, and currently used in multiple IRB approved protocols completed or in process at DUSOM (Pro00029516, Pro00040268, Pro00065334).

Furthermore, the therapeutic potential of rTMS has been limited by poor understanding of major factors determining its neural effects, including **stimulation frequency**, **spatial targeting**, and **brain state**. With respect to **frequency**, it is generally believed that low-frequency (~1Hz) rTMS produce inhibitory effects (Chen et al., 1997; Siebner et al., 1999; Muellbacher et al., 2000) and high-frequency rTMS (≥ 2Hz), excitatory effects (Fitzgerald et al., 2006; Leitao et al., 2013; Luber and Lisanby, 2014). However, there is evidence of low-frequency rTMS producing enhancements (Drager et al., 2004; Andoh et al., 2006; Andoh et al., 2008; Snyder, 2009; Caparelli et al., 2012) and high-frequency rTMS producing inhibition (Modugno et al., 2001; Lorenzano et al., 2002). Long rTMS trains are not optimal for interleaving rTMS with a behavioral task in order to modulate a specific neurocognitive process (Luber and Lisanby, 2014), and frequency effects for short rTMS trains (e.g., 3 seconds) could be quite different than for long rTMS trains. Also, it is unclear if the critical factor is the number of pulses or the duration of the pulse trains.

With respect to **spatial targeting**, it is now well established that the magnitude and direction of TMS effects on the brain depend not only on the temporal parameters of stimulation, but also on the spatial positioning of the TMS coil. Spatial coil positioning is one of the most critical decisions in the TMS parameter space, and it can partly explain differences in TMS efficacy (Fitzgerald et al., 2009; Sack et al., 2009). The effects of TMS coil positioning depend on the individual brain anatomy and the spatial distribution of the induced E-field, which determines what neural populations are affected (Peterchev et al., 2012). Thus, simulation of the E-field induced by TMS in individual subjects is increasingly recognized as an essential step in spatial targeting of specific brain regions. Furthermore, the selective effect of local TMS on brain systems could be associated, in part, to patterns of connectivity between regions. Given that rTMS modulates not only the local cortical target areas, but also distant regions connected to it (Andoh et al., 2015; Muldoon et al., 2016), another major factor is the structural (white-matter) connectivity of the stimulated brain region. DWI tractography can measure structural connectivity but it has been rarely used in conjunction with E-field modeling to predict the effect of TMS (Opitz et al., 2016).

With respect to **brain state**, though there is abundant evidence that the effects of TMS interact with the state of the brain, the underlying neural mechanisms remain uncertain (Bestmann and Feredoes, 2013; Miniussi et al., 2013; Bergmann et al., 2016). At least three different paradigms have been employed, yielding different effects. *First*, studies that used rTMS and manipulated brain state with a sensorimotor or cognitive task have usually found that task-related activity potentiates rTMS effects. For example, MEPs elicited by M1 TMS are larger when participants instructed to contract the muscle before TMS is applied imagine themselves performing the action (Clark et al., 2003; Stinear and Byblow, 2003), or observe someone else performing it (Fadiga et al., 1995; Strafella and Paus, 2000). In a *second* paradigm of studies, single-pulse TMS studies have found that suppressing activity in a subpopulation of neurons with priming or adaptation tends to enhance their sensitivity to TMS (Silvanto et al., 2007; Cattaneo and Silvanto, 2008). *Lastly*, studies that manipulated brain state with TMS or tDCS prior to TMS find that previous stimulation can reverse TMS effects (Lang et al., 2004; Siebner et al., 2004; Silvanto et al., 2008; Silvanto and Pascual-Leone, 2008). In sum, although there is ample evidence that brain state plays a profound role in the magnitude and direction of TMS effects, the underlying neural mechanisms are not well understood.

The current project will build on our existing knowledge for neurostimulation (Protocol 00065334), and therefore aims to resolve three interlocking problems in the design and

application of rTMS: timing, spatial targeting, and interactions with brain state. In 3 Studies, neuronal responses to rTMS will be quantified in humans as they perform a visual motion task that allows systematic manipulation of brain activity and cognitive state. We will focus on a specific motion-selective brain area, MT, and the circuits that connect with it. **First**, we will determine the effects of timing on the pulse sequences delivered during rTMS. We will systematically trade off frequency with number of pulses delivered as participants perform the task and brain activity and behavioral performance are monitored. Definitive dose-response relationships for rTMS temporal parameters will be established for both species. **Second**, we will assess simple but principled methods for spatial targeting of distributed networks. Based on imaging of white-matter connectivity and computational models of rTMS-induced neural activation, we will examine how location and orientation of the TMS coil differentially recruits two major pathways, the dorsal and ventral streams of the visual system. **Third**, we will tackle the fundamental question of how rTMS interacts with endogenous activity in the brain. By manipulating task demands, we will systematically control brain state and quantify how this alters the influence of rTMS on neural activity and cognitive performance. Taken together, this project will yield a multi-scale data set with a series of experiments that should generalize well to the study of other cerebral cortical circuits and provide insight into the optimal use of TMS for clinical and therapeutic goals.

4. Design & Procedures:

The study procedures outlined below cover 3 integrated experiments. A general overview of each study suggests a highly integrated set of experiments that will help explain neuromodulatory effects. **Study 1** investigates the effects of **frequency** and number of pulses, manipulated across blocks. rTMS is applied to MT or the vertex at 7 doses consisting of up to 30 pulses at 1, 5, or 10Hz. **Study 2** manipulates the **location** and orientation of the coil during rTMS of MT to bias rTMS effects either toward the dorsal pathway or toward the ventral pathway. **Study 3** manipulates **brain state** and uses *motion task blocks*, as in Studies 1 and 2, but also *color task blocks* and *rest blocks*. As in Study 2, only 5Hz rTMS is used. Therefore, we describe first the *shared* design information, and then describe design information *specific* to each of the 3 Studies.

Table 1. TIMELINE OF STUDY PROCEDURES:

Assessment	Screening Session	Session 1 (Shared)	Session 2 or 3 TMS-fMRI	Session 2 or 3 TMS-EEG
1. Subject consent & questionnaires	X			
2. Urine Test	X			
3. Practice with Motion task	X			
4. TMS Tolerability	X			
5. TMS Motion disruption, phosphene and motor thresholds	X			
6. Structural MRI (T1 & DWI)		X		
7. Resting-state fMRI		X		
8. Event-related fMRI with Motion task		X		
9. Concurrent TMS-fMRI with Motion task			X	
10. Concurrent TMS-EEG with Motion task				X
11. Side Effect Checklist	X		X	X

The Table above presents the timeline of major study procedures.

Shared Design Details

Subject Screening. In each of the 3 studies proposed, 48 different healthy young adults (18-30 y.o.) will participate in both TMS-MRI and TMS-EEG components of each study. Participants will have no psychiatric or neurological history and no ongoing psychoactive drug use (for more details see Section 5 below). Normal right-handed volunteers will be recruited from the community.

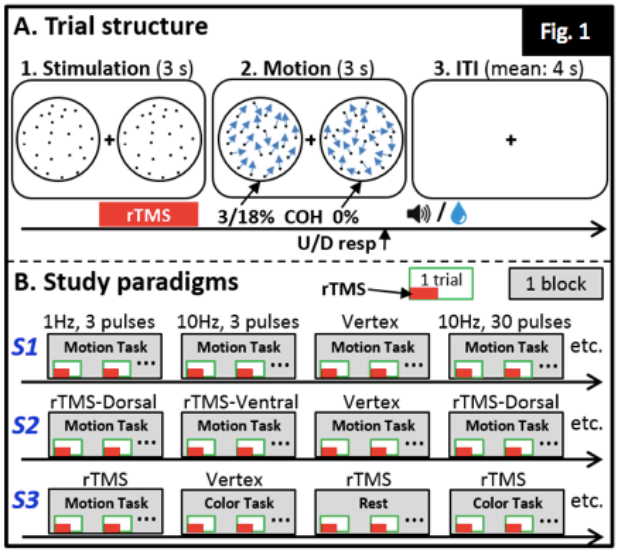
Each participant will take part in up to **seven** sessions: the first two sessions are *shared* by the TMS-MRI and TMS-EEG components of each study. The third and fourth sessions correspond separately to the TMS-fMRI and TMS-EEG sessions—with designs specific to each of the 3 Experiments—with the order counterbalanced across participants. If participants have been included in the pilot protocol, they will have two additional visits. Finally, an additional visit is built in if subjects need to make up a visit (e.g. poor task performance).

Shared Session 1: Screening. During Session 1 participants will be screened for the study with the rTMS screening forms (demographics, health, etc.), BIAC screening form, and a urine test. If they pass the screening procedure, they will proceed to the to the TMS Service Center, where motor threshold will be defined; and where they will learn and practice the motion tasks used in the study (about 0.5 hr) during visual cortex stimulation in order to acclimate them to rTMS and to obtain phosphene, motion disruption thresholds, for future dosing of rTMS. The motion task in the screening visit will consist of the second phase (motion period) of the task described below.

Shared Session 2: MRI Scanning. During Session 2 (2 hrs), participants undergo a 60-min MRI session. At BIAC, after obtaining a structural MRI and DTI and resting-state fMRI scans, fMRI data will be recorded from subjects while they perform the Motion task. BOLD images will be acquired with a 3.0T GE MR Scanner. Stimuli will be back-projected onto a screen located at the head of the MRI bed using an LCD projector. Subjects will view the screen via a mirror system located in the head coil. Task onset will be electronically synchronized with the MRI acquisition computer.

Shared Motion Task: All three Studies use the same motion task but manipulate different factors. Every trial consists of three phases (**Fig. 1A**): stimulation, motion, and inter-trial interval. Here we describe the task with rTMS—practice versions and fMRI versions of the Motion Task are identical, minus the delivery of rTMS.

1. Stimulation period (3 s). Subjects view two circles on either side of fixation, each filled with stationary random dots, while receiving rTMS to right MT or vertex. When an rTMS burst is briefer than 3 s, its onset is delayed so it co-terminates with the stimulation period (e.g., a 1.5-s rTMS burst is delayed by 1.5 s). rTMS is delivered to MT at a value not to exceed 120% of



individualized motor threshold, an intensity that yields both inhibitory and excitatory effects for brief trains (Gerschlager et al., 2001; Modugno et al., 2001; Fitzgerald et al., 2002; Lang et al., 2006) and has been shown to be within the published safety guidelines (Rossi et al., 2009b).

2. Motion period (3 s). The dots inside both circles start moving. All dots in the right circle move randomly in all directions (0% coherence—COH). Most dots in the left circle move randomly, but a percentage of dots move upward or downward together. The percentage of dots moving together is either high (18% coherence) or low (3% coherence) to make the task easy or hard (~90% or 60% correct, respectively, where chance=50%) as established in our pilot studies (Britten et al., 1992). Subjects indicate as quickly as possible whether the coherently moving dots in the left circle moved upwards or downwards through responses on two different buttons. Dot motion continues for 3 s regardless of response time. After the motion period, feedback for correct vs. incorrect responses is delivered: high- vs. low-pitch sounds (corresponding to high vs. low monetary payoffs at the end of the study).

3. Inter-trial interval (ITI, mean: 4 s). Subjects maintain fixation on a central cross for a period varying between 2 and 7 sec (mean: 4 sec). This jittered ITI is critical for event-related fMRI analyses, but is also used to keep conditions identical.

Phosphene Threshold Determination: All rTMS procedures will occur in rooms 54210, 54211 and 54212 in the Department of Psychiatry and Behavioral Sciences, Duke Clinic South. Phosphene threshold is defined as the minimum magnetic flux needed to elicit phosphenes (the perception of moving lights in the absence of an actual visual stimulus) in 5 out of 10 trials. Like the motor threshold, phosphene threshold is a standard approach for determining the intensity of rTMS for each individual to reduce seizure risk. The phosphene threshold will be determined in a dark room using a blindfold to enhance the subject's ability to detect phosphenes. The presence of moving phosphenes will be identified by subject verbal response. The scalp region producing moving phosphenes will be identified and recorded on the BrainSight neuronavigation system. Phosphene and motion disruption threshold will be used to determine the exact location in V5 which is involved in motion perception; then intensity of stmulation over this specific area will be defined according to rMT. From this, we will confirm the target engagement.

Motor Threshold Determination: Motor threshold (MT) is defined as the minimum magnetic flux needed to elicit a threshold EMG response in a target muscle in 5 out of 10 trials. MT is the standard in the field for determining the intensity of rTMS for each individual to reduce seizure risk. The motor evoked potentials (MEP) for the contralateral first dorsal interosseus (FDI) will be measured with EMG. The scalp region producing the largest amplitude MEP will be identified and recorded on the BrainSight neuronavigation system. At that scalp location, the lowest rTMS intensity able to elicit 5 MEP's of ≥50μV in peak-to-peak amplitude in 10 trials at this site will be determined, using a descending method-of-limits procedure. MT will be determined for each hemisphere with the muscle at rest (verified by baseline EMG). Individual MT will be used to determine the intensity of stimulation for each individual, as recommended by safety guidelines.

***Concurrent TMS-fMRI* Procedure**. The TMS coil is positioned over the individual's marked right MT target site and locked into place using a coil holder (MagVenture). Subjects are then positioned in the bore of the MR scanner. Several interleaved TMS-fMRI runs are then performed. In each run, rTMS bursts are delivered on each trial (**Fig. 1B**) at a value not to exceed to 120% of the motor threshold. fMRI is acquired using a gradient echo sequence with the following imaging parameters: flip angle=77^{o},

TR=1750ms, TE=27ms, FOV=25.6 mm^2, and 39 4mm thick slices. These data are collected with a GE three-axis balanced-torque head gradient coil and a shielded end-capped quadrature transmit-receive birdcage radio frequency coil. A delay of 250 ms is inserted between each acquisition during which a single biphasic TMS pulse is delivered. To track the actual position of the coil during stimulation, four fiducial markers are placed on the coil. rTMS administration will be controlled by an external computer and will be time-locked relative to stimulus presentation. After the concurrent TMS-fMRI Session, a brief rTMS side effect rating scale and visual analog mood ratings will be administered before and after each rTMS block.

Subjects' side effects will be monitored closely. As indicated in the procedures section, side effects are assessed in a charted, structured interview both prior to and after the rTMS session. Subjects are informed of all known side effects during the consent process and during the rTMS sessions. They are further instructed during consenting and additionally at the conclusion of the rTMS session to contact the principal investigator or study physician with any questions or concerns (including those that may arise after the experimental session has ended).

Concurrent TMS-EEG **Procedure.** Before stimulating, the optimal right MT target is identified with fMRI activation and E-field modeling (see TMS setup in MRI-TMS, above), and co-registered on the subject structural MRI using the Brainsight neuronavigation system (Rogue Research, Montreal). Stimulation intensity is set on the MagPro R30 stimulator (MagVenture, Alpharetta, GA) at intensities scaled on motion disruption or motor thresholds.

Continuous EEG is recorded at 5000Hz with a 64-channel BrainAmp DC TMS-compatible EEG system (BrainProducts LLC, Morrisville, NC). The EEG cap is placed on the subjects' head and electrode impedances are adjusted before the start of each session to be less than 5kOhms. A figure 8 magnetic coil (A/P-MCF-B65, MagVenture) is placed as close as possible to the scalp (over the EEG electrodes) and held in place with a Robotic Arm System (RAS: Advanced Neuro Technology Co., Enschede, Netherlands), which provides precise fMRI-guided rTMS coil placement. The RAS, combined with a neuronavigation system (Brainsight Frameless, Rogue Research, Montreal, QC, Canada) automatically navigates the coil to cortical targets on the individual's 3-dimensionally rendered brain MRI with less than one millimeter error, and dynamically moves the coil to safely track with slight head movements in less than 0.3 seconds with millimeter precision while the subject performs the task. At the start of the experiment, the spatial location of each electrode is digitized and aligned on each individual's anatomical scan. After the concurrent TMS-EEG Session, a brief rTMS side effect rating scale and mood ratings will be administered before and after each rTMS session. Side effects will continue to be monitored throughout the procedure.

Table 2. Conditions in Study 1

Cond	Sites	Hz	Sec.	Pulses
1	MT	1	3.0	3
2	MT	5	3.0	15
3	MT	10	3.0	30
4	MT	10	1.5	15
5	MT	10	0.3	3
6	Vtx	1	3.0	3
7	Vtx	10	3.0	30

Specific Study Design Information

Study 1

Study 1 investigates the effects of **frequency** and number of pulses, manipulated across blocks. Table 2 describes the 7 conditions used in this experiment. rTMS is applied to MT or the vertex at 7 doses consisting of up to 30 pulses at 1, 5, or 10Hz. In conditions 1–3, these frequencies are delivered for 3 seconds leading to 3, 15, and 30 pulses, respectively. In conditions 4 and 5, frequency remains at 10Hz, but durations are 1.5 and .3 seconds, respectively, to yield

numbers of pulses that match conditions 1 and 2. Thus, we manipulate frequency while keeping duration constant, and number of pulses while keeping frequency constant. In control vertex stimulation conditions 6 and 7, rTMS is delivered for 3 seconds at 1Hz or 10Hz, matching the pulses of conditions 1 and 3, respectively.

Each of the 7 conditions is assigned to two blocks of 20 trials each (40 trials/condition); each trial lasts 10 seconds, and we will administer 14 blocks (47 minutes, 280 trials total) in both the TMS-fMRI and TMS-EEG experiments. The TMS-fMRI and TMS-EEG will necessitate 60 minutes preparation to adjust the positioning for the TMS coil and—in the TMS—EEG experiment—apply the EEG cap, as well as 30 minutes for a brief rTMS side effect rating scale and visual analog mood ratings will be administered before and after each rTMS block. Thus, the entire session will last 3 hours for both the TMS-fMRI and TMS-EEG Session. As above, subjects' side effects will be monitored closely, and all side effect monitoring described above will be repeated. Furthermore, all intensities fall within the rTMS safety guidelines (Rossi et al., 2009b).

Study 2

Study 2 manipulates the location and orientation of the coil during rTMS of MT to bias rTMS effects either *toward the dorsal pathway* (**rTMS-D**) or *toward the ventral pathway* (**rTMS-V**). Positioning parameters are chosen by integrating information about (1) white-matter connectivity for ventral/dorsal pathways from MT, and (2) the induced E-field from MRI-based individual head models and its relationship to functional activity. First, fMRI maps are used to select the stimulation site, which is the seed point for E-field estimation. Next, DWI tractography estimates from the stimulation site, MT, are used to define trajectories of fiber tracts from MT into the dorsal pathway, specifically to FEF, or into the ventral pathway, specifically to the anterior temporal lobe. Then, structural scans (T1- and T2-weighted) are used for E-field modeling to select the best coil orientations for aligning the E-field distribution along the dorsal or ventral pathways identified above on an individual basis.

Thus, Study 2 uses 3 spatial conditions for rTMS stimulation. Each of the 3 conditions is assigned to four blocks of 20 trials each (80 trials/condition); each trial lasts 10 seconds, and we will administer 12 blocks (40 minutes, 240 trials total) in both the TMS-fMRI and TMS-EEG experiments. The TMS-fMRI and TMS-EEG will necessitate 60 minutes preparation to adjust the positioning for the TMS coil and—in the TMS—EEG experiment—apply the EEG cap, as well as 30 minutes for a brief rTMS side effect rating scale and visual analog mood ratings will be administered before and after each rTMS block. Thus, the entire session will last 3 hours for both the TMS-fMRI and TMS-EEG Session. As above, subjects' side effects will be monitored closely.

Study 3

Study 3 manipulates **brain state** and uses *motion task blocks*, as in Studies 1 and 2, but also *color task blocks* and *rest blocks* (**Fig. 1B**). As in Study 2, only 5Hz rTMS is used. Study 3 crosses stimulation site (rTMS to MT vs. vertex) and brain state (motion, color, rest). The color task starts like the motion task but, instead of moving, the dots change color. In both left and right circles, the dots are all grey during the stimulation period and turn blue or red during the "color period" (equivalent to the motion period). On the right side, 50% turn red and 50% blue, but on the left side, there is a greater proportion of blue or red dots. Subjects will press keys to report the more prevalent color. Difficulty is manipulated by varying the proportions of blue vs. red dots, which are titrated to match the difficulty of 3% vs. 18% motion coherence conditions. During rest blocks, participants rest while maintaining fixation.

Study 3 uses 6 conditions (Stimulation Site [vertex, target] x Brain State [color task, motion task, rest]) for rTMS stimulation. Each of the 6 conditions is assigned to three blocks of 20 trials each (60 trials/condition); each trial lasts 10 seconds, and we will administer 12 blocks (60 minutes, 360 trials total) in both the TMS-fMRI and TMS-EEG experiments. The TMS-fMRI and TMS-EEG will necessitate 60 minutes preparation to adjust the positioning for the TMS coil and—in the TMS—EEG experiment—apply the EEG cap, as well as 30 minutes for a brief rTMS side effect rating scale and visual analog mood ratings will be administered before and after each rTMS block. Thus, the entire session will last 3 hours for both the TMS-fMRI and TMS-EEG Session. As above, subjects' side effects will be monitored closely.

Piloting

Piloting of the Motor Tasks and rTMS: In order to ensure success of the design proposed above, it will be critical to determine the proper timing of the rTMS effect. It is critical to determine the optimum stimulation onset to provide the maximal benefit to participants' working memory performance. As such, we plan to recruit 264 younger adults in an abbreviated version of the design for each Study presented above (88 participants per Study). Study procedures will be **identical** to those described above in **Table 1**, excluding Steps 6-10, which include MRI scanning. We will therefore rely on a non-MRI-based 10-20 system; while not as effective as fMRI-based targeting, using the 10-20 system for TMS positioning is applicable at low cost and may reach desired cortex regions reliably on a larger scale level (Herwig et al., 2003). Timing parameters for each piloting session are identical to those described above for **Study1/Study2/Study3**.

5. Selection of Subjects:

In each of the 3 studies proposed, 48 healthy young adults (18-30 y.o.) will participate in both TMS-MRI and TMS-EEG components of each study.

Study Inclusion Criteria:

1. Age restrictions
    a. Age between 18-30.
2. Use of effective method of birth control for women of childbearing capacity.
3. Willing to provide informed consent.

Study Exclusion Criteria (ascertainment when appropriate):

1. Current or recent (within the past 6 months) of substance abuse or dependence, excluding nicotine and caffeine (urine test).
2. Current serious medical illness (self report).
3. History of seizure except those therapeutically induced by ECT (childhood febrile seizures are acceptable and these subjects may be included in the study), history of epilepsy in self or first degree relatives, stroke, brain surgery, head injury, cranial metal implants, known structural brain lesion, devices that may be affected by rTMS or MRI (pacemaker, medication pump, cochlear implant, implanted brain stimulator); [TMS Adult Safety Screening (TASS) form].
4. Subjects are unable or unwilling to give informed consent.
5. Diagnosed any Axis I DSM-IV disorder (MINI, DSM-IV)
6. Subjects with a clinically defined neurological disorder including, but not limited to:
    a. Any condition likely to be associated with increased intracranial pressure
    b. Space occupying brain lesion.
    c. History of stroke.

d. Transient ischemic attack within two years.
e. Cerebral aneurysm.
f. Dementia.
g. Mini Mental Status Exam (MMSE) score of <24.
h. Parkinson's disease.
i. Huntington's disease.
i. Multiple sclerosis.

7. Increased risk of seizure for any reason, including prior diagnosis of increased intracranial pressure (such as after large infarctions or trauma), or currently taking medication that lowers the seizure threshold.
8. Subjects with cochlear implants
9. Subjects not willing to tolerate the confinement associated with being in the MRI scanner.
10. Women who are pregnant or breast-feeding (urine test).
11. Blindness.
12. Inability to read or understand English.

6. Subject Recruitment & Compensation:

We will recruit 264 total subjects into our 3 Studies. Prior to the main experiment for each Study, we will recruit pilot subjects to refine the experimental procedure and ensure adequate power (n=40 for each of 3 Studies, n=120 total). Then, for the main experiments, 48 subjects will be recruited for each study (n=144 total). Thus, 48 volunteers will be recruited for each Study, half male, half female, in order to achieve three groups of 38 completers for each study, given a 20% drop-out rate.

Subject Recruitment: Neurologically normal volunteers will be recruited from either a subject pool maintained at the BIAC for MRI (IRB protocol Pro00010672), the IBRC SONA site, Duke List (www.dukelist.edu), Craigslist, or flyers distributed on campus locations. Additionally, subjects who have participated in another active TMS Study (Protocol 000065334) and have explicitly indicated a willingness to be contacted for future experiments, may be contacted for participation in the current protocol. Male and female subjects from all racial and minority groups will be accepted.

Subject payment: $20 per hour, approximately $300.00 total for screening session (2 hrs), MRI session (2 hrs), and up to 4 additional sessions pairing TMS with another data collection technique (2 hrs each). 15 hours represents the maximum possible participation, including piloting and the full study, with the possibility of making up one visit. Payment will be made by via direct deposit for individuals with a Duke Unique ID or by check sent by mail within a few weeks after the end of their study involvement.

7. Consent Process:

Section 14 questions have been completed on the e-IRB submission form.

8. Subject's Capacity to Give Legally Effective Consent:

N/A: Only involves healthy volunteers

9. Study Interventions:

TMS and MRI procedures presented in #4 above.

10. Risk/Benefit Assessment:

There are no known long-term health risks to the use of either MRI or EEG when operated within FDA guidelines. However there are safety concerns posed by the strong magnetic fields used to make images collected with MRI. All scans conducted under this protocol meet the FDA's guidelines for non-significant risk for static field strength, specific absorption rate (SAR), time varying magnetic fields (dB/dt), and acoustic noise.

There are no known long-term health risks to the use of rTMS per se when operated within consensus safety guidelines (Rossi et al., 2009). The Duke Medical Center Institutional Review Board recently classified two similar research applications of rTMS proposed by the PI as a "non-significant risk" (Protocols 65334 and 24349). In 2008, the FDA approved the use of high frequency rTMS in the treatment of depression. Also in 2008, an international consensus conference on safety guidelines for rTMS met, including a representative from our own lab (Dr. Peterchev). Their report (Rossi et al., 2009) systematically reviewed the thousands of healthy subjects and patients who have undergone rTMS in order to allow for a better assessment of relative risks. The relative infrequency of adverse events using rTMS was noted. They concluded that in the case of Class 3 studies (studies involving indirect benefit and low risk in normal subjects and patients that are expected to yield important data on brain physiology or safety, but have no immediate relevance to clinical problems), normal volunteers should be permitted to participate in rTMS research when it is likely to produce data that are of outstanding scientific or clinical value. They also concluded that this research can be performed in a non-medical setting (i.e., psychology labs, robotics labs, research institutions, etc. as opposed to a hospital or appropriately equipped outpatient clinic). The Rossi et al. consensus report went on to suggest safety guidelines based on the now rather extensive international experience with rTMS. These guidelines include the rTMS intensity and timing parameters considered safe, training, and planning for and managing emergencies. We will follow these guidelines, and have incorporated them into our screening and session procedures. The consensus safety guidelines (Rossi et al., 2009a) are included as a Study Documents attachment with this IRB application.

Participation is voluntary, and there will be no pressure or time constraints regarding the decision to participate. There are no benefits to the participants except for the monetary reward or compensation, as well as the good will of helping the progress of scientific research. The information learned from this study may aid our understanding of the mechanisms of action underlying TMS and the dose-response relationships between stimulation and neural activity.

<u>MRI Adverse Events Plan:</u>

An MRI procedure is considered to be "minimal risk" according to federal definitions. To date, no after effects have been revealed and the FDA has classified the MR procedure as possessing a "non significant risk" for the subject of study. To minimize risks, all subjects will be screened for metallic devices, implants and other contraindications to scanning. Women of child-bearing capacity will be evaluated for pregnancy using a urine pregnancy test prior to scanning. Those unlikely to tolerate the sense of confinement during scanning will also be excluded.

Adequate safety monitoring and observation during scanning will be provided, as will measures to enhance the subject's physical and emotional comfort during the scan. It is possible that some subjects might experience minor distress by the confined and noisy conditions in the scanner. This possibility will be minimized by earplugs and headphones, and experienced technicians who will monitor all subjects for distress. In the event that a subject becomes anxious during a scan, the study will be halted. Subjects will be able to communicate with the investigators at all times using the intercom system should they wish to request that a study be terminated or have

concerns or questions during the procedure. The subject is in full view of the operator at all times.

The probability of an incidental finding that might lead to the diagnosis of an unknown abnormality is greater than zero. All subjects will be alerted to this possibility during the consent process. In that event, subjects or their designated physician will be provided copies of their anatomical scans and advised to seek further evaluation if they have concerns.

EEG Adverse Events Plan

EEG entails the passive recording of electrical activity generated by the brain. The EEG signal is recorded from 64 electrodes embedded in an elastic cap worn by the participant. To create a high-quality conductive connection between the scalp and the electrodes, each electrode is filled with a conductive gel. The skin is gently rubbed to remove the top layer of dead skin cells in order to make a good conductive connection. Due to isolation and grounding safety mechanisms, the risk of electrical shock with our FDA-approved EEG system is negligible. There is only one main potential risk. *Potential risk of skin discomfort*. There is the possibility of slight discomfort during the fitting of the electrode cap and associated preparation of the skin. Participants are asked to let the experimenters know if they experience any discomfort during skin preparation, so that the experimenters can modify their technique. They are also informed that they may experience minimal redness or discomfort at the site of the electrodes later on, which usually clears up without intervention within a day or two. If participants report continued discomfort, the study session will be terminated and the participant will be dismissed with compensation.

TMS Adverse Events Plan:

Seizure is a theoretical risk with rTMS. In the Rossi et al. report it was stated that "The occurrence of seizures has been extremely rare, with most of the few new cases receiving rTMS protocols exceeding previous guidelines, often in patients under treatment with drugs which potentially lowered the seizure threshold." As Rossi et al. delineate, "rare" means that 16 cases (out of tens of thousands of rTMS sessions over the last two decades) of seizure related to rTMS have been reported. Eight occurred before safety parameters were established in 1997. Of the other eight reports, six occurred either when the safe rTMS parameters were exceeded or other safety guidelines ignored, and the actual occurrence of a seizure has been questioned in the other two (i.e., convulsive syncope or pseudoseizure may have occurred). In a workshop convened by the National Institute for Neurological Disorders and Stroke (NINDS) in 1996, researchers in the field agreed upon a set of *rTMS consensus safety guideline*s, including recommended stimulation parameters and contra-indications (Wassermann, 1998), and these consensus guidelines have been recently updated (Rossi et al., 2009). Widespread adherence to the 1996 guidelines has resulted in the virtual elimination of inadvertent seizures in rTMS studies (Rossi et al., 2009). The levels of stimulation used in this protocol are well within safety guidelines (Rossi et al., 2009; Wassermann et al. 1998).

We will screen subjects for known risk factors for seizure with rTMS (medical screening and medical history). Personnel who administer rTMS are trained to recognize a potential seizure event and to act as "first responders" in order to administer appropriate initial care. All study personnel have undergone Basic Life Saving training, and seizure-specific training. The major physical signs the study personnel will look out for in detecting a potential seizure include chewing movements,

convulsions/tremor/shaking, difficulty talking, a blank stare, eyes rolling up, and profuse sweating. If any of these signs are observed, study personnel will stop the research procedure and inquire whether the subject feels okay. If the subject is unresponsive (and therefore likely experiencing a seizure), first-aid will be supplied. The first-aid response consists of making sure the subject is physically safe for the duration of the seizure. This involves moving the subjects out of the rTMS chair and onto the floor lying down on his or her left side. The subject will be kept lying down on his or her left side, while the staff call emergency medical help, via a 911 call. Resources available in the laboratory include a first-aid kit and immediate phone access. A seizure constitutes a reportable adverse event, and will thus be immediately reported to the IRB via the Safety Events Form mechanism.

The most commonly reported side effect of rTMS is headache. This headache is typically of a muscle-tension type. It usually develops during or immediately after the stimulation and may last for minutes to hours following the end of the stimulation. It is typically limited to the day of stimulation, and usually responds promptly to single doses of over–the-counter pain medications. Neck pain or scalp pain may also occur. Both are usually managed easily with over-the-counter analgesics.

As noted in Rossi et al. (2009), Loo and colleagues reported mild and transient changes in auditory threshold in two depressed patients following a 2-4 week rTMS course of rTMS (Loo et al., 2001). Cases of tinnitus have been reported after rTMS treatments. In addition, in a recent study investigating the effects of rTMS on symptoms of depression, a patient experienced moderate to severe tinnitus after an rTMS session in which earplugs were not used. Rossi et al. recommended that hearing protection always should be worn during rTMS application, and that individuals with cochlear implants not receive rTMS. In the current study, earplugs will be worn by all subjects during rTMS procedures. Individuals with cochlear implants will be excluded from participation.

Risks to the unborn children of pregnant women receiving MRI and rTMS are unknown. Pregnant women will be excluded as per IRB policy. Female subjects are tested once with a urine pregnancy test prior to their first MRI session as per IRB-approved BIAC policy. These female subjects agree not to become pregnant while remaining within the subject pool, and to notify the experimenter or subject coordinator if they become pregnant. If sexually active, the subject must agree to use appropriate contraceptive measures for the duration of the study. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. If the subject has any uncertainty about whether they could be pregnant, another urine pregnancy test will be performed before they can participate in this protocol. The person(s) who will perform the urine pregnancy test will have successfully completed training as directed by the Chair of Obstetric and Gynecology of the Duke University School of Medicine. The urine pregnancy test kits used for this research study will be those commercially available test kit specified by the Chair of Obstetric and Gynecology and in routine use at DUHS.

11. Costs to the Subject:

There is no cost for subjects to participate in this study.

12. Statistical Analysis Plan:

Shared Analytical Procedures

fMRI analyses. fMRI data are inspected for head motion and data quality using custom BIAC software. Multiple regression analyses use FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) FEAT tool (FMRI Expert Analysis Tool). Physiological noise is accounted for in our models by using FSL's PNM toolbox, with a model optimized for brainstem signals. Initial multiple regression analyses are conducted on individual runs, and then across runs for individuals participants using a fixed-effects analysis. These analyses are combined across participants within each group using random-effects analyses implemented via FSL's FLAME tool. Between-group comparisons are controlled for multiple comparisons using an FDR alpha set to < 0.05.

EEG analyses. Pre-processing of EEG includes bad channel replacement, temporal filtering, and ICA analyses to remove artifacts. EEG analyses use either repeated-measures ANOVAs or non-parametric methods(Maris and Oostenveld, 2007b, a) to infer amplitude and latency effects on relevant ERP components and/or sources, as described in each study. Coherence analyses are performed to estimate inter-channel connectivity, with planned analyses on cross-hemispheric and anterior-posterior associations. As done in our past studies,(Appelbaum et al., 2006; Appelbaum et al., 2008; Appelbaum et al., 2010; Ales et al., 2012; Appelbaum et al., 2012) depth-weighted minimum norm analyses will be performed using MRI-derived finite element head models calculated for each participant following alignment of electrode positions to the MRI head surface. Head models are based on compartmentalized tissue segmentations that defined contiguous regions for the scalp, outer skull, inner skull, and the cortex. Cortically constrained minimum norm source estimates are determined by a linear optimization of dipole magnitudes with the least total (root mean square) power while lead field normalization is used to compensate for the inherent bias toward superficial sources.

Specific Study Analytical Procedures

Study 1

TMS data: Mixed model ANOVAs with repeated-measures factors of Frequency (1Hz/5Hz/10Hz), and Number of Pulses (3/15/30 pulses), and rTMS (target, sham [vertex] stimulation) will be performed separately on the median RT and accuracy data. Power analysis shows that 30 subjects/group should be sufficient to see a medium sized effect at an alpha of 0.05. In our previous studies using a Working Memory task with active and sham rTMS over multiple sites, letter set sizes, and task phases, groups of 21 (Luber et al., 2007) 15 (Luber et al., 2008) and 26 (Luber et al., 2013) were sufficient to produce significant effects at the 0.05 level.

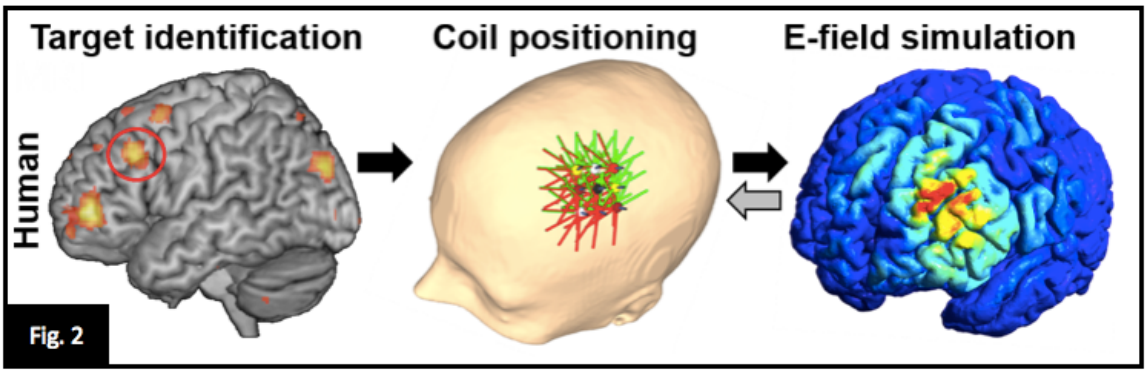
Study 2

DWI fiber tracking. Our DWI tractography methods have been reported (Davis et al., 2009). For a priori tracts connecting the MT cortex, we use TrackVis (trackvis.org) to identify MT and all connecting regions (FEF, IPS).(Kier et al., 2004b, a) FA values are extracted and analyzed using standard statistics.

Functional connectivity. Task-related functional interactions are estimated using the beta-series correlations (Rissman et al., 2004; Daselaar et al., 2006). Functional matrices are then evaluated for descriptive graph-theoretical properties (e.g., node degree) using the Brain Connectivity Toolbox (http://www.brain-connectivity-toolbox.net). This method has been described before by us (Davis et al., 2012) and others (Fornito et al., 2011; Betzel et al., 2014).

E-field Modeling. Study 2 will rely on the creation of anatomically realistic E-field models of transcranial electric and magnetic stimulation (**Fig. 2**). T1- and T2-weighted

MRI scans are acquired with isotropic voxel resolution of 1 mm. DWI data are obtained with resolution of 2 mm.



Modeling*:* Head regions are extracted from MRI images, then up-sampled, reoriented, corrected for bias field inhomogeneity, filtered with content-preserving anisotropic diffusion filters, and automatically segmented with software (including gray matter, white matter, and CSF using SPM). High resolution triangular surface meshes of the head model (SimNIBS) are used to compute the E-field (Windhoff et al., 2013). A detailed model of the TMS coil is added to the head model (**Fig. 2**, center). Isotropic tissue conductivities are assigned to the various tissue compartments.(Opitz et al., 2011) Optionally, we can include anisotropic conductivity in the white matter based on the DWI data, although the impact of white matter anisotropy is small for TMS which affects predominantly superficial cortex (Opitz et al., 2011; Lee et al., 2012). The E-field is computed with a harmonic solver in Maxwell using FEA and scaled in post-processing for the specific pulse shape and amplitude (Deng et al., 2011). ***Using the models for targeting***: For SCR in the TMS-induced E-field, the TMS coil will be oriented so that the modeled E-field is normal to the sulcal wall nearest to the recording target to achieve strongest neural activation (Janssen et al., 2014, 2015). For TMS during fMRI or EEG, the peak voxel of fMRI task activation (**Session 2**) will be used as the center of a 3×3 (A-P and L-R) grid for positioning the coil in simulations of the E-field (**Fig. 2**, right) corresponding to these 9 coil positions and 6 orientations (54 combinations). The simulation E-field maps will be extracted and correlated, voxel-to-voxel, with the fMRI activation to determine an optimal coil orientation and position. The simulation that yields the highest correlation is selected the optimal coil position and orientation.

Study 3

fMRI Analyses: All EEG, fMRI and behavioral analysis approaches described above will be implemented. However, a unique feature of Study 3 is that it will examine multiple brain states (motor task, color task, rest), while Study 1 and 2 focus on the motor task along. We will therefore capture the cross-task similarities using Independent Components Analysis (ICA), which is useful for identifying consistent relationships between disparate datasets.

TMS data: Mixed model ANOVAs with repeated-measures factors of Site (2 scalp locations, target or vertex), and Brain State (color, motion task, or rest) will be performed separately on the median RT and accuracy data.

13. Data & Safety Monitoring:

The subjects will be fully informed of the nature of the study requirements prior to enrollment and periodically throughout the study. The subject's wellbeing will be continuously monitored by the experimenter, and the Principal Investigator will report all

serious adverse events in an expedited manner to the Duke University Health System (DUHS) Institutional Review Board (IRB) office and all applicable regulatory authorities in accordance with the Center's standard operating procedures.

The study monitor will be Dr. Lawrence G. Appelbaum. Dr. Appelbaum will ensure the quality of the study and establish that each co-investigator is complying with the investigational plan and IRB regulations. Monitoring of this protocol is simplified by the fact that this study involves a small number of investigators and a single facility in which the study is being conducted.

Throughout the investigation, the monitor will ensure that the facilities being used continue to be acceptable for the purposes of the study, that the investigational plan is being followed, that any changes to the protocol have received IRB approval and have been reported to the sponsor, that accurate, complete, and current records are maintained, that accurate, complete, and timely reports are made to the IRB. This will be accomplished through quarterly meetings during which the status of the protocol, investigators, and IRB compliance are reviewed. The monitor will review each research chart for completeness and accuracy. He will confirm that inclusion and exclusion criteria have been met for each subject enrolled, and compliance with all other aspects of the investigational plan are met.

14. Privacy, Data Storage & Confidentiality:

Section 12 of the e-IRB submission form have been completed.

Words Cited

Ales JM, Farzin F, Rossion B, Norcia AM (2012) An objective method for measuring face detection thresholds using the sweep steady-state visual evoked response. J Vision 12.

Andoh J, Matsushita R, Zatorre RJ (2015) Asymmetric Interhemispheric Transfer in the Auditory Network: Evidence from TMS, Resting-State fMRI, and Diffusion Imaging. J Neurosci 35:14602-14611.

Andoh J, Artiges E, Pallier C, Riviere D, Mangin JF, Paillere-Martinot ML, Martinot JL (2008) Priming frequencies of transcranial magnetic stimulation over Wernicke's area modulate word detection. Cerebral cortex 18:210-216.

Andoh J, Artiges E, Pallier C, Riviere D, Mangin JF, Cachia A, Plaze M, Paillere-Martinot ML, Martinot JL (2006) Modulation of language areas with functional MR image-guided magnetic stimulation. Neuroimage 29:619-627.

Appelbaum LG, Ales JM, Norcia AM (2012) The Time Course of Segmentation and Cue-Selectivity in the Human Visual Cortex. Plos One 7.

Appelbaum LG, Ales JM, Cottereau B, Norcia AM (2010) Configural specificity of the lateral occipital cortex. Neuropsychologia 48:3323-3328.

Appelbaum LG, Wade AR, Vildavski VY, Pettet MW, Norcia AM (2006) Cue-invariant networks for figure and background processing in human visual cortex. J Neurosci 26:11695-11708.

Appelbaum LG, Wade AR, Pettet MW, Vildavski VY, Norcia AM (2008) Figure-ground interaction in the human visual cortex. J Vision 8.

Bergmann TO, Karabanov A, Hartwigsen G, Thielscher A, Siebner HR (2016) Combining non-invasive transcranial brain stimulation with neuroimaging and electrophysiology: Current approaches and future perspectives. Neuroimage 140:4-19.

Bestmann S, Feredoes E (2013) Combined neurostimulation and neuroimaging in cognitive neuroscience: past, present, and future. In: Year in Cognitive Neuroscience (Miller MB, Kingstone A, eds), pp 11-30.
Betzel RF, Byrge L, He Y, Goni J, Zuo XN, Sporns O (2014) Changes in structural and functional connectivity among resting-state networks across the human lifespan. Neuroimage 102 Pt 2:345-357.
Britten KH, Shadlen MN, Newsome WT, Movshon JA (1992) THE ANALYSIS OF VISUAL-MOTION - A COMPARISON OF NEURONAL AND PSYCHOPHYSICAL PERFORMANCE. J Neurosci 12:4745-4765.
Caparelli EC, Backus W, Telang F, Wang GJ, Maloney T, Goldstein RZ, Henn F (2012) Is 1 Hz rTMS Always Inhibitory in Healthy Individuals? The Open Neuroimaging Journal 6:69-74.
Cattaneo Z, Silvanto J (2008) Investigating visual motion perception using the transcranial magnetic stimulation-adaptation paradigm. Neuroreport 19:1423-1427.
Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, Cohen LG (1997) Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 48:1398-1403.
Clark L, Manes F, Nagui A, Sahakian BJ, Robbins TW (2003) The contributions of lesion laterality and lesion volume to decision-making impairment following frontal lobe damage. Neuropsychologia 41:1474-1483.
Daselaar SM, Fleck MS, Prince SE, Cabeza R (2006) The medial temporal lobe distinguishes old from new independently of consciousness. J Neurosci 26:5835-5839.
Davis SW, Kragel JE, Madden DJ, Cabeza R (2012) The Architecture of Cross-Hemispheric Communication in the Aging Brain: Linking Behavior to Functional and Structural Connectivity. Cerebral cortex 22:232-242.
Davis SW, Dennis NA, Buchler NG, White LE, Madden DJ, Cabeza R (2009) Assessing the effects of age on long white matter tracts using diffusion tensor tractography. Neuroimage 46:530-541.
Deng ZD, Lisanby SH, Peterchev AV (2011) Electric field strength and focality in electroconvulsive therapy and magnetic seizure therapy: a finite element simulation study. Journal of Neural Engineering 8.
Drager B, Breitenstein C, Helmke U, Kamping S, Knecht S (2004) Specific and nonspecific effects of transcranial magnetic stimulation on picture-word verification. Eur J Neurosci 20:1681-1687.
Fadiga L, Fogassi L, Pavesi G, Rizzolatti G (1995) MOTOR FACILITATION DURING ACTION OBSERVATION - A MAGNETIC STIMULATION STUDY. Journal of Neurophysiology 73:2608-2611.
Fitzgerald PB, Fountain S, Daskalakis ZJ (2006) A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clinical Neurophysiology 117:2584-2596.
Fitzgerald PB, Brown TL, Daskalakis ZJ, Chen R, Kulkarni J (2002) Intensity-dependent effects of 1 Hz rTMS on human corticospinal excitability. Clinical Neurophysiology 113:1136-1141.
Fitzgerald PB, Hoy K, McQueen S, Maller JJ, Herring S, Segrave R, Bailey M, Been G, Kulkarni J, Daskalakis ZJ (2009) A Randomized Trial of rTMS Targeted with MRI Based Neuro-Navigation in Treatment-Resistant Depression. Neuropsychopharmacology 34:1255-1262.

Fornito A, Yoon J, Zalesky A, Bullmore ET, Carter CS (2011) General and Specific Functional Connectivity Disturbances in First-Episode Schizophrenia During Cognitive Control Performance. Biological Psychiatry 70:64-72.
Gerschlager W, Siebner HR, Rothwell JC (2001) Decreased corticospinal excitability after subthreshold 1 Hz rTMS over lateral premotor cortex. Neurology 57:449-455.
Herwig U, Satrapi P, Schonfeldt-Lecuona C (2003) Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. Brain Topogr 16:95-99.
Janssen AM, Oostendorp TF, Stegeman DF (2014) The effect of local anatomy on the electric field induced by TMS: evaluation at 14 different target sites. Medical & Biological Engineering & Computing 52:873-883.
Janssen AM, Oostendorp TF, Stegeman DF (2015) The coil orientation dependency of the electric field induced by TMS for M1 and other brain areas. Journal of Neuroengineering and Rehabilitation 12.
Kier EL, Staib LH, Davis LM, Bronen RA (2004a) Anatomic dissection tractography: A new method for precise MR localization of white matter tracts. American Journal of Neuroradiology 25:670-676.
Kier EL, Staib LH, Davis LM, Bronen RA (2004b) MR imaging of the temporal stem: Anatomic dissection tractography of the uncinate fasciculus, inferior occipitofrontal fasciculus, and Meyer's loop of the optic radiation. American Journal of Neuroradiology 25:677-691.
Lang N, Siebner HR, Ernst D, Nitsche MA, Paulus W, Lemon RN, Rothwell JC (2004) Preconditioning with transcranial direct current stimulation sensitizes the motor cortex to rapid-rate transcranial magnetic stimulation and controls the direction of after-effects. Biological Psychiatry 56:634-639.
Lang N, Harms J, Weyh T, Lemon RN, Paulus W, Rothwell JC, Siebner HR (2006) Stimulus intensity and coil characteristics influence the efficacy of rTMS to suppress cortical excitability. Clinical Neurophysiology 117:2292-2301.
Lee WH, Deng ZD, Kim TS, Laine AF, Lisanby SH, Peterchev AV (2012) Regional electric field induced by electroconvulsive therapy in a realistic finite element head model: influence of white matter anisotropic conductivity. Neuroimage 59:2110-2123.
Leitao J, Thielscher A, Werner S, Pohmann R, Noppeney U (2013) Effects of Parietal TMS on Visual and Auditory Processing at the Primary Cortical Level - A Concurrent TMS-fMRI Study. Cerebral cortex 23:873-884.
Loo C, Sachdev P, Elsayed H, McDarmont B, Mitchell P, Wilkinson M, Parker G, Gandevia S (2001) Effects of a 2- to 4-week course of repetitive transcranial magnetic stimulation (rTMS) on neuropsychologic functioning, electroencephalogram, and auditory threshold in depressed patients. Biol Psychiatry 49:615-623.
Lorenzano C, Gilio F, Inghilleri M, Conte A, Fofi L, Manfredi M, Berardelli A (2002) Spread of electrical activity at cortical level after repetitive magnetic stimulation in normal subjects. Exp Brain Res 147:186-192.
Luber B, Lisanby SH (2014) Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS). Neuroimage 85 Pt 3:961-970.
Luber B, McClintock SM, Lisanby SH (2013) Applications of transcranial magnetic stimulation and magnetic seizure therapy in the study and treatment of disorders related to cerebral aging. Dialogues in clinical neuroscience 15:87-98.
Maris E, Oostenveld R (2007a) Nonparametric statistical testing of EEG- and MEG-data. Journal of neuroscience methods 164:177-190.

Maris E, Oostenveld R (2007b) Nonparametric statistical testing of EEG- and MEG-data. Journal of Neuroscience Methods 164:177-190.
Miniussi C, Harris JA, Ruzzoli M (2013) Modelling non-invasive brain stimulation in cognitive neuroscience. Neuroscience & Biobehavioral Reviews 37:1702-1712.
Modugno N, Nakamura Y, MacKinnon CD, Filipovic SR, Bestmann S, Berardelli A, Rothwell JC (2001) Motor cortex excitability following short trains of repetitive magnetic stimuli. Exp Brain Res 140:453-459.
Muellbacher W, Ziemann U, Boroojerdi B, Hallett M (2000) Effects of low-frequency transcranial magnetic stimulation on motor excitability and basic motor behavior. Clinical Neurophysiology 111:1002-1007.
Muldoon SF, Pasqualetti F, Gu S, Cieslak M, Grafton ST, Vettel JM, Bassett DS (2016) Stimulation-Based Control of Dynamic Brain Networks. PLOS Computational Biology 12:e1005076.
Opitz A, Windhoff M, Heidemann RM, Turner R, Thielscher A (2011) How the brain tissue shapes the electric field induced by transcranial magnetic stimulation. Neuroimage 58:849-859.
Opitz A, Fox MD, Craddock RC, Colcombe S, Milham MP (2016) An integrated framework for targeting functional networks via transcranial magnetic stimulation. Neuroimage 127:86-96.
Peterchev AV, Wagner TA, Miranda PC, Nitsche MA, Paulus W, Lisanby SH, Pascual-Leone A, Bikson M (2012) Fundamentals of transcranial electric and magnetic stimulation dose: Definition, selection, and reporting practices. Brain Stimul 5:435-453.
Rissman J, Gazzaley A, D'Esposito M (2004) Measuring functional connectivity during distinct stages of a cognitive task. Neuroimage 23:752-763.
Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMSCG (2009a) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 120:2008-2039.
Rossi S et al. (2009b) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clinical Neurophysiology 120:2008-2039.
Sack AT, Kadosh RC, Schuhmann T, Moerel M, Walsh V, Goebel R (2009) Optimizing Functional Accuracy of TMS in Cognitive Studies: A Comparison of Methods. J Cogn Neurosci 21:207-221.
Siebner HR, Tormos JM, Ceballos-Baumann AO, Auer C, Catala MD, Conrad B, Pascual-Leone A (1999) Low-frequency repetitive transcranial magnetic stimulation of the motor cortex in writer's cramp. Neurology 52:529-537.
Siebner HR, Lang N, Rizzo V, Nitsche MA, Paulus W, Lemon RN, Rothwell JC (2004) Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: Evidence for homeostatic plasticity in the human motor cortex. J Neurosci 24:3379-3385.
Silvanto J, Pascual-Leone A (2008) State-dependency of transcranial magnetic stimulation. Brain Topogr 21:1-10.
Silvanto J, Muggleton N, Walsh V (2008) State-dependency in brain stimulation studies of perception and cognition. Trends Cogn Sci 12:447-454.
Silvanto J, Muggleton NG, Cowey A, Walsh V (2007) Neural activation state determines behavioral susceptibility to modified theta burst transcranial magnetic stimulation. Eur J Neurosci 26:523-528.

Snyder A (2009) Explaining and inducing savant skills: privileged access to lower level, less-processed information. Philosophical Transactions of the Royal Society B-Biological Sciences 364:1399-1405.
Stinear CM, Byblow WD (2003) Motor imagery of phasic thumb abduction temporally and spatially modulates corticospinal excitability. Clinical Neurophysiology 114:909-914.
Strafella AP, Paus T (2000) Modulation of cortical excitability during action observation: a transcranial magnetic stimulation study. Neuroreport 11:2289-2292.
Wassermann EM (1998) Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalography and clinical neurophysiology 108:1-16.
Windhoff M, Opitz A, Thielscher A (2013) Electric field calculations in brain stimulation based on finite elements: An optimized processing pipeline for the generation and usage of accurate individual head models. Hum Brain Mapp 34:923-935.