Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Wiley Interdiscip Rev Cogn Sci. Author manuscript; available in PMC 2021 October 18.

Published in final edited form as:

Wiley Interdiscip Rev Cogn Sci. 2021 July ; 12(4): e1553. doi:10.1002/wcs.1553.

Combining transcranial magnetic stimulation with functional magnetic resonance imaging for probing and modulating neural circuits relevant to affective disorders

Desmond J. Oathes,
Center for Neuromodulation in Depression and Stress, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine

Nicholas L. Balderston,
Center for Neuromodulation in Depression and Stress, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine

Konrad P. Kording,
Depts of Neuroscience and Bioengineering, University of Pennsylvania

Joseph A. DeLuisi,
Center for Neuromodulation in Depression and Stress, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine

Gianna M. Perez,
Center for Neuromodulation in Depression and Stress, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine

John D. Medaglia,
Department of Psychology, Drexel University; Department of Neurology, Drexel University; Department of Neurology, Perelman School of Medicine, University of Pennsylvania

Yong Fan,
Center for Biomedical Image Computing and Analytics (CBICA), Department of Radiology, University of Pennsylvania Perelman School of Medicine

Romain J. Duprat,
Center for Neuromodulation in Depression and Stress, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine

Theodore D. Satterthwaite,
Lifespan Informatics and Neuroimaging Center, University of Pennsylvania Perelman School of Medicine

Yvette I. Sheline,
Center for Neuromodulation in Depression and Stress, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine

oathes@pennmedicine.upenn.edu .

Desmond J. Oathes, no conflicts.

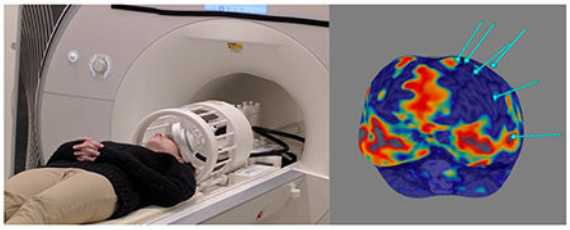
Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Kristin A. Linn
Center for Neuromodulation in Depression and Stress, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine; Penn Statistics in Imaging and Visualization Center, University of Pennsylvania Perelman School of Medicine, Department of Biostatistics, Epidemiology, and Informatics; Center for Biomedical Image Computing and Analytics, University of Pennsylvania Perelman School of Medicine

Abstract

Combining transcranial magnetic stimulation (TMS) with functional magnetic resonance imaging (fMRI) offers an unprecedented tool for studying how brain networks interact *in vivo* and how repetitive trains of TMS modulate those networks among patients diagnosed with affective disorders. TMS compliments neuroimaging by allowing the interrogation of causal control among brain circuits. Together with TMS, neuroimaging can provide valuable insight into the mechanisms underlying treatment effects and downstream circuit communication. Here we provide a background of the method, review relevant study designs, consider methodological and equipment options, and provide statistical recommendations. We conclude by describing emerging approaches that will extend these tools into exciting new applications.

Graphical Abstract



Combining non-invasive brain stimulation with functional neuroimaging offers mechanistic insights into brain network communication, circuit-level descriptions of neuropathology, and an opportunity for personalized treatment development.

1. INTRODUCTION

Neuroimaging is being used to explore affective and cognitive systems in increasingly sophisticated ways, but inroads into refining or improving treatments for neuropsychiatric conditions based on this research are few and remain largely descriptive rather than clinically actionable. The mismatch between systemic treatments such as medications or psychotherapy and measurements of brain activity at some snapshot in time or in response to a specific task likely contributes to suboptimal understanding of how these treatments work. In the case of brain stimulation interventions, there is an unparalleled opportunity to validate explicit models of mechanistic changes in brain networks that putatively contribute to clinical outcomes. Brain stimulation is by its nature a brain-based intervention and we have a variety of imaging tools to examine changes in the brain underlying clinical improvement. Neuroimaging can also be used as baseline predictors for defining more individualized treatments. The recent development of transcranial magnetic stimulation (TMS) coils that

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

can be safely operated in a magnetic resonance imaging (MRI) environment and that do not cause excessive signal loss gives rise to a variety of intriguing new investigations. TMS is a form of non-invasive brain stimulation that rapidly depolarizes cells below the coil and that can be applied in trains of stimulation to cause sustained changes in neural circuits (repetitive TMS or 'rTMS'). Functional MRI (fMRI) uses a blood oxygen level dependent (BOLD) contrast to define which brain areas are especially active during an experimental condition (or rest) across the brain. Combining these tools enables exploration of causal brain circuit interactions (validating network theories), measurement of plastic communication changes in targeted circuits, and quantification of how TMS treatments mechanistically change the brain. More broadly, interleaved TMS/fMRI adds causal circuit mapping to traditional imaging-only studies that suffer from problematic attributions of causality, reverse inference, and related weaknesses in interpretation (Dubois & Adolphs, 2016; Jonas & Kording, 2017; A. T. Reid et al., 2019).

Under a set of reasonable assumptions, the TMS/fMRI combination allows a direct measurement of the individual-level causal brain effects of stimulating an accessible region of the cortex. For clinical treatments it is especially worthwhile to know if manipulating a particular brain region will alleviate a clinical problem. As such, it is important to have causal information, which can, arguably, not be provided by observational methods (Marinescu, Lawlor, & Kording, 2018). TMS signals, undeniably, produce a locally focused perturbation of the brain. Provided they are given at random points of time, so that there is no association between brain state and presence of stimulation, individual-level causal effects can be identified and estimated. Despite technical challenges, combining neuroimaging with non-invasive brain stimulation *in vivo* with awake humans promises to provide unprecedented causal insights.

Lastly, we often want to change behavior by changing the brain through various stimulation approaches. This leads to an immediate optimization problem: finding which stimulation protocol will lead to maximal effects in target brain areas underlying behavioral abnormalities. Solving this problem at the brain level requires varying the stimulation parameters and measuring resulting brain responses. As such, combining TMS and fMRI provides a strategy to control neural activity and test causal theories with clear downstream opportunities for clinical applications of TMS in affective disorders and other neuropsychiatric conditions.

To facilitate a better understanding of how TMS/fMRI is conducted, what questions it can address, and the state of the field with current applications, these topics will be addressed in the following sections. An emphasis will be placed on applications relevant to treating affective disorders, anxiety, and PTSD given our research focus. However, the concepts are easily extrapolated to other disorders and cognitive neuroscience applications.

2. TMS/FMRI DEVELOPMENT AND BASIS

A fundamental challenge in combining TMS with fMRI is that TMS coils were originally made from highly ferromagnetic materials. The TMS coil itself was ultimately redesigned with copper litz wire which is safe in the MRI bore (Bohning et al., 1999). To reduce

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

noise in the MR signal, additional filters reduced direct current flowing in the wires (a source of noise) and RF filtering was added. To accommodate the actual stimulator being in a room adjoining the MRI room, a much longer set of cables join the TMS coil to the stimulator and are connected through a wave guide to allow the TMS coil to be placed on the scalp of participants in the MRI bore. Early studies established the technical possibility of the method and described the effects of TMS stimulation in local and distal brain regions. An important initial study used interleaved TMS/fMRI with stimulation over the motor cortex in human participants, and found dose dependent effects of TMS with higher amplitude stimulation associated with increased BOLD signal locally and remote to the site of stimulation (Bohning et al., 1999).

In order for TMS to be used to understand brain function, it was important to demonstrate that TMS evoked brain responses are similar in nature to other functional assays typically recorded with brain imaging. Initial TMS/fMRI work demonstrated, for example, that TMS evoked hemodynamic responses were similar to those recorded during a motor and cognitive fMRI task (Bohning et al., 1999). Local and distal effects of repetitive TMS on fMRI signals have also been shown to be stimulation level dependent (Bestmann, Baudewig, Siebner, Rothwell, & Frahm, 2005). The strength of using hemodynamic recordings to describe brain responses to TMS has been supported as well by combined neural recordings and tissue oxygen measurements in non-human animals revealing spiking, local field potential increases and a neuronal coupling response to brief trains of repetitive TMS (Allen, Pasley, Duong, & Freeman, 2007). Single pulse TMS also causes stimulation intensity dependent evoked responses in human EEG (Komssi, Kähkönen, & Ilmoniemi, 2004) and neural firing in non-human primate parietal cortex (Romero, Davare, Armendariz, & Janssen, 2019). Thus, the field now has established that TMS evoked brain responses can be reliably detected using established imaging tools.

While human TMS/fMRI studies began with studies of the motor cortex, clinical success in treating depression with prefrontal rTMS, e.g. (O'Reardon et al., 2007) especially focused attention on the prefrontal cortex. Stimulating left prefrontal cortex in healthy human subjects with interleaved fMRI shows that increased TMS amplitudes are associated with increased brain activity ipsilaterally as well as bilaterally (Nahas et al., 2001). More recent examples have also confirmed both local and remote brain responses to TMS of the prefrontal cortex (Hawco et al., 2018; Vink et al., 2018). Even when TMS targeting is done without precise anatomical or functional targeting, variability in TMS evoked fMRI responses reveal a diversity of 'propagation pathways' (Vink et al., 2018). Our own work suggests that TMS/fMRI can be useful to augment understanding from neuroimaging studies of brain circuits and networks with clinical relevance. For example, we showed that a correlation between brain areas from a task-based imaging study involved a circuit through which causal communication between nodes was possible as confirmed using a parallel interleaved TMS/fMRI experiment (Fonzo, Goodkind, Oathes, Zaiko, Harvey, Peng, Weiss, Thompson, Zack, Mills-Finnerty, et al., 2017). We've also shown an association between subcortical TMS evoked fMRI BOLD and treatment outcome following psychotherapy for PTSD (Fonzo, Goodkind, Oathes, Zaiko, Harvey, Peng, Weiss, Thompson, Zack, Lindley, et al., 2017). Finally, we have supported within network connectivity caused by stimulating a single node (brain region) of a network and causal antagonism between brain networks using

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

interleaved TMS/fMRI to measure brain evoked responses (Chen et al., 2013). In short, stimulation outside of the motor cortex is now not only possible but demonstrates utility in understanding brain network communication with clinical relevance.

Complex behaviors relevant to affective disorders undoubtedly depend on brain network communication. This communication can only be indirectly inferred from purely behavioral studies that do not also include imaging. In terms of evaluating behavioral effects of TMS, studies without neuroimaging do not allow for the full picture of how TMS impacts the brain (Ruff, Driver, & Bestmann, 2009). To address this shortcoming, targeted investigations that utilize TMS/fMRI explore causal relationships among various brain networks. For example, making use of both single pulse TMS and low frequency rTMS, it was concluded that the default mode network was regulated by the central executive network (Chen et al., 2013), which advanced the field over prior purely correlational imaging studies. A focus on brain network interactions with TMS is especially relevant to the increasing number of neuropsychiatric conditions that are being described as a consequence of brain network dysfunction. Prominent networks found to be abnormal in affective disorders include the default mode, salience, reward and executive control networks with specific areas such as the amygdala, hippocampus, inferior frontal gyrus, dorsal anterior cingulate cortex, dorsolateral prefrontal, insula and medial prefrontal cortex implicated (A. Etkin & Wager, 2007; McTeague et al., 2020; Rolls et al., 2019; Williams, 2017). This is not a definitive list and certainly depends on symptoms that overlap across disorders such as depression, generalized anxiety disorder and PTSD including concentration problems, sleep disturbance, anhedonia and negative affect. Of course, these networks and brain regions have direct and indirect connections which makes any determination of a causal hierarchy challenging. Understanding control regions (hubs) and network interactions is essential for designing new brain-based treatments. TMS/fMRI is well positioned to describe communication dysfunction in brain networks as well as to measure changes in brain network communication resulting from interventions thought to affect brain circuitry.

A variety of designs and applications combining TMS with fMRI are possible that capitalize on the use of TMS as a circuit probe, a neuromodulation tool, or both.

3. TMS/FMRI DESIGNS and APPLICATIONS

There are a variety of ways to combine TMS with fMRI to answer questions about causal circuit mapping, effects of neuromodulation, or to measure changes in a circuit in response to an intervention. Stimulations from TMS are rapid as single pulses and often include gaps between trains in neuromodulatory protocols (repetitive TMS; rTMS) allowing a variety of image sampling relative to TMS delivery. On the other hand, fMRI allows relative spatial precision for measuring brain responses that is driving our understanding of how stimulation interacts with endogenous brain activity. Unique study designs are possible that address these questions as explained below and followed up upon in the Future Directions section. TMS administered adjacent to the scanner and with pre and post imaging is the technically least challenging way to combine these technologies.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

3.1 fMRI->rTMS->fMRI

A lab with access to an MRI scanner and TMS equipment can readily accommodate an experimental design that acquires fMRI data before and after neuromodulation with repetitive TMS (rTMS). rTMS is administered as a series of TMS trains with fixed frequencies and gaps delivered over time ranges from seconds to minutes designed to have a sustained influence (excitatory/inhibitory) on brain activity. The pre and post fMRI scans can be acquired within a single session to measure acute changes to fMRI readouts, or can be done before and after an intervention demonstrating symptom changes over time. Task as well as resting fMRI, ASL, spectroscopy, MRI compatible EEG, etc. scans can be used to demonstrate reactivity or connectivity changes induced by rTMS.

The most obvious analysis in this design would be to measure neuromodulatory effects associated with the site of stimulation, such as seeding the site of stimulation to measure change in connectivity strength from pre to post-rTMS. The measured change comparing these two timepoints is assumed to be caused by the application of neuromodulation. This makes intuitive sense because the site of stimulation was directly manipulated with rTMS indicated by evidence from electric field models, electrophysiology, electroencephalography, motor evoked potentials and blood oxygen consumption describing rTMS effects on local activity at the site of stimulation (Allen et al., 2007; Hamidi, Slagter, Tononi, & Postle, 2009; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005; Mueller et al., 2014). Nevertheless, to attribute the change to the rTMS influence on brain circuits (rather than change in non-specific effects of applying TMS) requires careful control conditions to rule out confounds in explaining any observed changes (see Control Condition Sidebar). Even an electrical ‘sham’ stimulation of the scalp will have a biological effect that needs to be ruled out. Comparing pre to post-rTMS imaging data has shown clinically relevant findings such as an acute change in medial prefrontal to amygdala resting connectivity following a single round of rTMS (Riedel et al., 2019) as well as a change in subgenual cingulate to default mode connectivity after a clinical dose of rTMS treatment in depression (Liston et al., 2014). In the latter study, rTMS was applied to the dorsolateral prefrontal cortex (DLPFC) but the connectivity changes between the sgACC and DMN were associated with depression improvement. In terms of network architecture, this might mean that the DLPFC is a TMS accessible pathway to the sgACC but that the actual mechanism of clinical change is the connectivity changes this protocol induces between the two remote brain areas. This finding might suggest that the sgACC is a more critical communication ‘hub’ involved in maintaining depression as opposed to the DLPFC which also frequently shows abnormal activation in depression. Connectivity of distributed brain networks, best measured with online imaging, may be the most relevant mechanism of brain changes in response to rTMS that drive symptom improvement. Whether changes are found in the site of stimulation, e.g. (Nettekoven et al., 2014) or in remote brain areas (Liston et al., 2014; Riedel et al., 2019), it is possible to conclude that the changes demonstrate brain areas that are part of the causal pathway of the stimulation site due to the knowledge of where stimulation was applied (with caveats for unmeasured confounds; see Control Condition Sidebar). Adding neuroimaging recordings following neuromodulation is the only way to know the extent to which brain networks responded to the neuromodulation. These measurements can be used to understand

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

mechanisms of behavioral changes by quantifying the relationship between imaging and behavior changes.

The drawbacks of this design include that it takes time to bring the participant out of the bore of the scanner, walk to an adjacent room for rTMS, then to set them back up in the scanner again. This costs money for reserving the MRI slot and costs time during which acute plasticity effects are wearing off while participants are being set back up in the scanner. This time gap also may lose an opportunity to capture rapid oscillatory changes that are larger in magnitude. An additional consideration is that measures such as resting fMRI do not necessarily agree with direct brain stimulation measures, the latter being presumably most relevant to understanding TMS effects on the brain. For example, negative correlations are present in resting electrocorticography (ECoG) brain surface electrode recordings (and resting fMRI) but are absent when electrical brain stimulation is administered in conjunction with the ECoG recordings (Keller et al., 2011; Keller et al., 2013). These limitations can be addressed by applying TMS directly in the scanner and recording fMRI BOLD responses resulting from TMS pulses. Combining fMRI BOLD recordings with additional MR and MR compatible (non-MRI) measures can also add to our understanding of neuromodulatory effects of TMS. These additional imaging modalities will be more sensitive to oscillations and dynamics (EEG), neuronal effects (ASL), or relative concentrations of neurotransmitters (spectroscopy), complementing interpretations of the causal mechanisms of behavioral changes.

3.2 Interleaved spTMS/fMRI

Delivering single TMS pulses interleaved with fMRI recordings do not alone demonstrate neuromodulatory influences, but may nevertheless help to identify brain response that contribute to TMS treatment outcomes. Similar to a motor evoked potential, fMRI readouts can be used to indicate what brain areas are in the causal downstream path of the stimulated brain area. These connections can be multi-synaptic but given the control of where stimulation is applied, an argument is made that there is a directional communication link between the stimulated brain area and the downstream evoked brain response. Interleaving single TMS pulses with fMRI recordings is a powerful way to map functional brain circuit communication in awake healthy and/or patient populations. The single pulses are spaced out such that there is negligible neuromodulation (no persistent or cumulative effects) and to allow for fMRI readouts of whole brain responses to stimulation ‘probes’ applied to any surface accessible brain region. When targeting brain networks, it is necessary only to find a node (one brain region in a network) for that network at the brain surface which is possible for a full range of canonical networks in popular modern brain atlases, e.g. (Hagmann et al., 2008; Kong et al., 2019; Power et al., 2011; Schaefer et al., 2018). This strategy thus allows a completely non-invasive probe-and-record mapping of the downstream causal brain network for each node accessible to TMS.

For example, one study in our lab sought to understand the relationship between the fronto-parietal/central executive network and the default mode network (Chen et al., 2013), which is widely implicated in affective neuropathology (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; Sheline et al., 2009; Williams, 2016; Xia et al., 2018) as well as a

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

possible mechanism of clinical response to TMS (Liston et al., 2014). Neuroimaging on its own can only demonstrate a correlational relationship between these putative antagonistic systems. Using single pulse interleaved TMS/fMRI, we showed that FpN/CEN stimulation with TMS induced causal negative connectivity (psychophysiological interaction) between this system and the DMN (Chen et al., 2013) in support of the hypothesized relationship from imaging data alone. Other possible applications include being able to 'probe' a specific circuit believed to mechanistically contribute to treatment outcomes in affective disorders before and after the treatment is delivered. This strategy allows observations of the change in communication between the surface node and any remote target or set of targets associated with treatment-induced changes in clinical features. In a related possible application, researchers have begun to associate the stimulated brain network (based on normative data) with specific symptoms that were mitigated to generate a symptom change map from existing TMS treatment outcome data (Siddiqi et al., 2020). Adding TMS/fMRI measurements to these outcome data could help understand which symptom/brain networks respond to TMS and inform how the brain changes contribute to clinical improvements in specific symptom clusters. This type of evidence would help elucidate how changes in communication flow from the site of stimulation possibly contribute to remediating symptoms.

3.3 Interleaved spTMS/fMRI->rTMS-> interleaved spTMS/fMRI

Interleaved single pulse TMS/fMRI mapping can also be done before and after any intervention purported to target a specific pathway in order to map changes in the strength of connectivity in that pathway putatively caused by the intervention. To capture immediate circuit changes following the application of rTMS, single pulse TMS/fMRI can be administered before and after rTMS is delivered – all in the MRI bore. The outcome variable of interest in this case would be the difference in evoked brain response to single pulse TMS after compared with before neuromodulation. It is essential to ascribe the change to rTMS by comparing this difference to that obtained using a control condition (see Control Condition sidebar). An innovation in TMS equipment for the MRI environment (www.magventure.com) allows compressed air to be pushed through the windings of the TMS coil to cool it down and allow high frequency as well as theta-burst rTMS protocols in the bore of the MRI. Besides saving time on the scanner clock and reducing the time between rTMS delivery and fMRI readouts, the TMS coil and participant can be kept in the same position during the pre-rTMS interleaved spTMS/fMRI, rTMS and post-rTMS interleaved spTMS/fMRI scans, minimizing potential shifts of the TMS coil off of the optimal scalp position. In addition, rTMS protocols often include gaps between trains during which fMRI recordings can be made that allow a parametric analysis of dose to be calculated as the number of trains accumulates during rTMS administration. A recent intermittent theta-burst (iTBS) rTMS study that used functional near-infrared spectroscopy observed that the blood oxygenation response recorded between trains of rTMS was a more sensitive indicator of activation from iTBS than the blood oxygenation response recorded at rest following rTMS, and this relationship was stronger when using an active stimulation compared to sham stimulation (Struckmann, Persson, Weigl, Gingnell, & Bodén, 2020).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

4. CONDUCTING EXPERIMENTS

4.1 Implementation

A variety of additional peripheral equipment such as EEG, visual task displays, psychophysiology and the like can also be included in TMS/fMRI experiments but integration especially related to the timing of psychological events and multi-modal recordings is essential. Specifically, conducting task-based TMS/fMRI sessions requires tight synchronization between the task computer, display, response devices, TMS hardware, MRI scanner, and any additional devices (e.g. tactile stimulator, psychophysiology monitoring hardware, etc.). One approach to managing this complexity is to designate the task computer as the host device, with all other devices playing a passive role. The key to this approach is to control the timing of all devices using the standard 8-bit parallel port of the task computer, which uses standard 5V transistor-transistor-logic (TTL) digital signals to communicate with downstream devices. Most major experimental design programs (i.e. Presentation, Eprime, Psychopy, Psychotoolbox, etc.) have dedicated system functions for writing to the parallel port, and most major TMS devices (e.g. MagVenture, MagStim, etc.) and experimental stimulation (e.g. Digitimer, MEDOC, etc.) or recording devices (e.g. Biopac, etc.) can be controlled using TTL pulses via standard Bayonet Neill–Concelman (BNC) connectors. The benefit to this approach is that the parallel port provides a continuous synchronized 8-bit stream that can control these external devices in real time, and each bit can be turned on or off independently, allowing for control of up to 8 independent devices (e.g. TMS device on one bit, scanner on another bit) or experimental conditions (e.g. face [0] vs. house [1] coded as a single bit). When paired with a high-resolution psychophysiology monitoring system that records from all 8 bits, it is possible to have a precise record of the timing of all important events in the experiment. This degree of control is fundamental to integrating TMS with complex fMRI study designs.

Controlling electronic components for a precision TMS/fMRI experiment can also be done in other ways. An alternative to the above setup would be to use a separate microcontroller to control downstream devices. Like a computer parallel port, devices like an Arduino microcontroller have 5V digital bits that can be used to control the scanner and TMS device. The benefit of using a microcontroller is that there is low system overhead, and an ability to precisely control the firmware running on the device, making precise timing possible. The drawback of using a microcontroller as the host device is that it is more difficult to interface with standard computer hardware, like the projector or button boxes, making it more difficult to use this setup for task based TMS/fMRI experiments. However, this may be an ideal setup for TMS/fMRI experiments where the subjects are at rest and not interacting with a specific task. Managing equipment and making tradeoffs for ease of use and precision allows for sophisticated designs that yield insight into how TMS affects the brain and nervous system.

4.2 Targeting

Choosing a cortical stimulation target is a critical first step in any TMS or TMS/fMRI project that depends heavily on the research question being explored. However, translating this theoretical target to a practical coil position on the individual research subject’s scalp is perhaps an even more important second step. The figure-8 is the most common coil

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

design used in TMS and the only design used currently in TMS/fMRI experiments, and the magnetic field generated by the coil decays with the square of the distance from the center point where the wings of the coil meet. Furthermore, past research has suggested that TMS-related effects decay linearly as a function of scalp-to-cortex distance (Stokes et al., 2007). Additionally, the current induced by the magnetic field generated by the coil is typically strongest in cortical structures that are perpendicular to the magnetic field (Balslev, Braet, McAllister, & Miall, 2007; Kammer, Beck, Thielscher, Laubis-Herrmann, & Topka, 2001). Accordingly, it is critical to define both the position and the orientation of the coil with respect to the cortical target. Much like an airplane, the position and orientation of the coil in 3D space can be described using 6 degrees of freedom. The position can be described using the X, Y, and Z coordinates of the center of the coil, while the orientation can be described using the roll, pitch, and yaw vectors of the coil face. Approaches to defining these degrees of freedom have become more sophisticated in recent years, and the exact approach can vary across cortical sites, research groups, and environments (i.e. lab vs. scanner). In spite of this variability, there are best practices that should be considered in any new project.

4.2.1 Position (X, Y, Z)—First, the cortical site chosen should allow for individual variability. Many recent studies have begun to use task-based (Balderston et al., 2020; Rose et al., 2016) and resting state fMRI (Balderston et al., 2020; Chen et al., 2013; Freedberg et al., 2019) to identify individual cortical targets thought to subserve functional properties of the brain. These approaches have the benefit of accounting for cross-subject variability in both cortical structure and localization of function. Accounting for this variability across subjects would likely reduce variability in TMS evoked effects. However, it may be optimal to limit anatomical variability using a pre-defined broad region of interest based on known anatomical landmarks or reliable group data, e.g. pilot data, meta-analysis, etc. (Balderston et al., in press). Allowing for at least some variability in TMS coil placement according to an individual fMRI peak or brain parcel is recommended especially compared with a target generated from a non-patient group average. There is no gold standard or ideal functional brain map. Instead, ideal functional brain representations should be determined according to the population and goals of the study (Bijsterbosch et al., 2020).

4.2.2 Orientation (Roll, Pitch, Yaw)—Once the cortical site is chosen and identified for a given subject, the next step is to position the TMS coil so that it maximizes current induced at the site. Roll and pitch can be defined tangent to the scalp. Yaw is often defined perpendicular to the gyral surface at the site of stimulation (Thielscher, Opitz, & Windhoff, 2011). A more sophisticated approach is to model the current induced in the cortex given a particular site and orientation of stimulation using individualized head models created from freely available software (Thielscher, Antunes, & Saturnino, 2015). These electric (e)-field models can then be conducted with multiple equally spaced yaw vectors as input, and then evaluated for efficacy. The user can then choose the yaw vector that induces the maximal amount of current in the site or region of interest (Balderston et al., in press).

It is often not possible to prospectively determine the coil orientation in many TMS/fMRI studies where small spaces in the MRI head coil limit the flexibility of coil placement.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

In such cases, retrospective e-field modelling can be done to assess the efficacy of the stimulation given the actual position and orientation of the coils.

5. STATISTICAL CHALLENGES AND OPPORTUNITIES

Methods for the design and analysis of fMRI studies are well-established and continue to be improved with respect to statistical and computational efficiency (Ashby, 2019; Cohen et al., 2017; Lindquist, 2008; Mejia, Yue, Bolin, Lindgren, & Lindquist, 2020). There are a number of ways in which employing rigorous design principles and advanced statistical methodology could elevate TMS/fMRI research, leading to new discoveries about affective disorders that translate to better treatment strategies.

5.1 Representative sampling

Affective disorders are known to present heterogeneously across different patients (Williams, 2017), including those defined by demographic, socioeconomic, clinical, and other characteristics (Nandi, Beard, & Galea, 2009). Using a common survey sampling technique, it is possible to weight observations in an analysis such that the sample is representative of the target population; this technique is known as raking (Brick & Kalton, 1996). Recently, work has shown that applying raking in an analysis of neuroimaging data to study neurodevelopment led to different estimates of the average age of cortical and sub-cortical maturation compared to an unweighted analysis (LeWinn, Sheridan, Keyes, Hamilton, & McLaughlin, 2017). For TMS/fMRI studies that have adequately large sample sizes, raking on variables such as age and sex to match a specific target population with a specified affective disorder may be one way to help increase the generalizability and replicability of results from TMS/fMRI studies.

5.2 Reliability and Replicability

Assessing and optimizing the reliability of TMS/fMRI measures at the individual level will be critical to the success of TMS for treating affective disorders. Intra-class correlation is a common measure used to assess reliability of repeated measures (Bartko, 1966, 1976; Bravo & Potvin, 1991; Shoukri, Donner, & El-Dali, 2013), but other measures exist that are more tailored to neuroimaging data (Shou et al., 2013). Studies of repeated TMS measures in healthy participants, older adults, and stroke patients demonstrate that TMS evoked motor responses are highly reliable with reported ICCs ranging from 0.79-0.99 (Hassanzahraee, Zoghi, & Jaberzadeh, 2019; Houde et al., 2018; Schambra et al., 2015; Vaseghi, Zoghi, & Jaberzadeh, 2015). Furthermore, efforts toward the personalization of TMS treatment using fMRI-guided choice of stimulation sites may suffer from two sources of variability affecting reliability: the functional connectivity map used to choose the stimulation site and the evoked TMS brain response. At the population level, reported activation peaks from multiple large fMRI studies have demonstrated non-negligible spatial variation (Geuter, Lindquist, & Wager, 2017) which could add uncertainty to the choice of stimulation location(s) to study in a TMS/fMRI experiment. Recent work on spatial confidence sets (Bowring, Telschow, Schwartzman, & Nichols, 2019) for peak activation may help TMS/fMRI researchers better quantify uncertainty regarding where to stimulate when attempting to treat a particular affective disorder by targeting a specific brain region to modulate. Moving forward, entire

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

studies should be dedicated to rigorously quantifying the reliability of TMS evoked fMRI brain responses. An initial study of TMS evoked EEG responses reported reliability of 0.80-0.95 (Kerwin, Keller, Wu, Narayan, & Etkin, 2018) which suggests promise for other imaging modalities such as fMRI. Besides validating this emerging imaging modality, reliability measures will enable future TMS/fMRI studies to be more accurately powered, saving resources in the long-term.

5.3 Data harmonization and normalization

A number of large-scale, multi-site neuroimaging studies exist for studying affective disorders (Oltedal et al., 2017; Trivedi et al., 2016). Efforts are emerging to increase statistical power for TMS studies by pooling individual, de-identified data across institutions (Corp et al., 2020). Multi-site TMS/fMRI studies will allow for increased representativeness and larger sample sizes for studying affective disorders, but data harmonization will be critical to ensure comparability across fMRI scanners and TMS equipment. Harmonization of neuroimaging data acquired from multiple scanners is an active area of methodological research (Dewey et al., 2019; Modanwal, Vellal, Buda, & Mazurowski, 2020; Pomponio et al., 2020; Wrobel et al., 2020; Zhu, Moyer, Nir, Thompson, & Jahanshad, 2019). ComBat is a technique adapted from statistical genomics that has been shown to effectively harmonize a number of imaging modalities (Beer et al., 2020; Fortin et al., 2018; Fortin et al., 2017), including functional connectivity measures obtained with fMRI (Yu et al., 2018). Using an empirical Bayesian approach that borrows information across imaging features, ComBat estimates and removes scanner location and scale effects while preserving biological variation. Extensions of the ComBat model specifically for evoked TMS response data would increase the likelihood that pooling TMS/fMRI data from different institutions will lead to more efficient, generalizable statistical inference rather than introducing non-biological nuisance variability.

In some settings, it may be important to normalize evoked TMS response imaging to a common scale or domain prior to group-level analyses. This could be accomplished by scaling each individual's evoked TMS image by the standard deviation computed from all voxels in the rest of the brain or transforming each individual's image to a quantile TMS response before performing group-level analyses. The former preserves global, directional effects (e.g., positive or negative BOLD signal changes), while the latter enables inference to focus on whether certain brain regions have a high or low evoked TMS response relative to the rest of the brain for each individual.

5.4 Study design considerations and reporting results

In general, parallel designs (between subjects) require a larger sample size than crossover (within subjects) studies for equivalent statistical power (Louis, Lavori, Bailar III, & Polansky, 1984). In crossover designs, participants act as their own control, minimizing variability in the outcome that may be attributable to demographic, clinical, and other baseline characteristics. However, crossover designs in affective disorders are susceptible to the effects of natural mood cycles and stressful life events common in this population (Dwan, Li, Altman, & Elbourne, 2019). Furthermore, if individual-level causal TMS effects differ by brain state (see Brain State sidebar) or by the amount of discomfort caused

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

by different sites, the order in which multiple stimulation sites are probed in a single session or across multiple sessions could influence within-subject comparisons of evoked TMS responses. A subject's acclimation to the single pulses, resulting in physiological and brain-state changes, could induce carryover effects that obscure the true underlying individual-level causal effect of stimulation location (Aguirre, 2007) as well. Tradeoffs between parallel and crossover designs for a particular experiment should be carefully considered during the study planning phase, ideally with the guidance of a statistician. For example, crossover studies may be susceptible to attrition, which could result in the study being underpowered and requiring careful consideration of missing data in the analysis.

Transparent reporting of TMS/fMRI studies will promote thorough understanding of the methods and increase the chance that results can be replicated by other researchers. The CONSORT checklist (http://www.consort-statement.org/) is a good starting point for information that should be included in manuscripts describing randomized trials. There is an increasing trend of including CONSORT diagrams in studies of affective disorders with neuroimaging (Mehler et al., 2018; Novaes et al., 2020; Siegle et al., 2012). A CONSORT diagram transparently reports the intended study population and actual analytic sample that remained after participants dropped out and poor-quality images were discarded. The imaging community has also published more specific guidelines for the reporting of neuroimaging studies to promote responsible, reproducible research (Poldrack et al., 2017; Poldrack et al., 2008). For example, containerized workflows can enhance reproducibility given the incredible diversity in preprocessing steps employed across labs with fMRI data (http://www.humanbrainmapping.org/files/2016/COBIDASreport.pdf). The TMS community could consider expanding upon similar guidelines to cover issues that are specific to TMS/fMRI experiments, such as how stimulation amplitude was determined, whether an individual or atlas target was used, whether single pulse or repetitive stimulation was delivered, gap sizes between imaging readouts, any randomization or blinding of stimulation sites, etc. Randomization lists can be generated to *a priori* allow for the option to recruit additional study participants at the end of the study without breaking the randomization, which may introduce bias. Blinding of the randomized treatment assignments is also advisable when possible. Study coordinators may also be blinded if another member of the team marks sites 'A,' 'B,' etc. instead of 'amygdala target,' 'subgenual cingulate target,' and so on.

6. FUTURE DIRECTIONS

For many advances in fMRI, there are related TMS/fMRI experiments that could be done to extend the knowledge gained from the imaging advances. For example, the field of real-time neurofeedback has pioneered approaches to rapidly calculate region of interest and whole-brain machine learning indicators of optimal brain states that are usually fed back to the participant visually. Using the same rapid analysis tools, it should be possible to change straightforward TMS parameters such as rTMS frequency or train length to optimize stimulation towards moving a specific brain target for an individual patient. Changing stimulation parameters based on the fMRI signal allows for a **closed-loop** approach to identifying an optimal set of stimulation parameters that may be circuit- or patient-specific.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Another approach for probing potential causal pathways is to use interleaved single pulse TMS/fMRI across a variety of potential targets. For example, one could evaluate several surface accessible functional connectivity-based peaks in order to see which modulates a specific downstream target (e.g. amygdala) or network (e.g. fronto-parietal) most effectively. Although there is time and expense for the MRI costs, this **pathway optimization** approach may reduce patient and clinician burden in conducting a full 4-6 week treatment that does not engage the intended circuit.

Combining TMS with fMRI also promises to **calibrate network science** approaches to delineate control centers of the brain that are effective in driving networks. A large field aims to estimate networks (Bassett & Sporns, 2017; Betzel, Avena-Koenigsberger, et al., 2016; Betzel, Gu, Medaglia, Pasqualetti, & Bassett, 2016; Wang, Zuo, & He, 2010) or, more precisely causal interactions (Andrew T Reid et al., 2019) from structural or fMRI recordings. Individualized imaging-based calculations are making strong links between network-based measurements and cognition as well as mental health (Cole, Braver, & Meiran, 2017; Cole, Repovš, & Anticevic, 2014; Dixon et al., 2018; Komssi et al., 2004; Mill, Ito, & Cole, 2017). Missing links to causal understanding of how the measurements and mental faculties correspond will benefit from informed manipulations of brain activity along with appropriate recordings. Only ground-truth data combined with formal causal reasoning and inference can ultimately support theoretical work and correlational imaging studies. The ability to combine stimulation and recording of brain activity promises a way of producing gold-standard data for unbiased estimation of causal effects, allowing researchers to test to which network science ideas are most supported by empirical experimental data. There are now multiple instances where network control measures derived from neuroimaging have been used to understand rTMS effects on behavior (Beynel et al., 2020; Lynch et al., 2019; Medaglia et al., 2018). Adding TMS/fMRI to these kinds of studies will give us greater evidence for the mechanisms by which stimulation to these nodes affects networks and behavior.

Finally, a lofty goal in affective disorders is to find **matches between stimulation targets** and specific symptom clusters, **patient** diagnoses, or brain-behavior ‘biotypes.’ Our prior work has shown that the comorbidity between depression and generalized anxiety disorder relates to a brain-behavior bio-type and that these biotypes are informative in determining which patients might respond to rTMS treatment delivered to a particular brain target (Drysdale et al., 2017). Similarly, preliminary work suggests that different brain networks targeted with rTMS might be able to move specific symptom based depressed patient clusters (Siddiqi et al., 2020).

Limitations to interleaved TMS/fMRI as an approach warrant discussion. In addition to a need for reliability measures, the actual correspondence between neural firing and TMS evoked changes in the brain are not fully characterized. For example, our finding that sgACC and amygdala targeting can evoke a negative fMRI BOLD response in both areas (Desmond J Oathes et al., 2018) does not answer what is happening at the level of neural firing or neurovascular coupling that explains the negative response. In terms of targeting, TMS is ideal for brain regions or network nodes that are at the surface of the cortex. It is not possible to directly manipulate subcortical-subcortical connections that could be highly

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

relevant to affective illness (Tye et al., 2011). Finally, there are a number of brain areas that will respond simply due to TMS being uncomfortable such as the dACC, insula, medial prefrontal cortex and brain stem. Overlap of these and other areas implicated in affective disorders complicates interpretation of the effects of TMS. Contrasting evoked responses at scalp locations with similar discomfort ratings may be a way to reduce the influence of TMS discomfort on effects of interest, but it is likely difficult to predetermine these optimal control sites before running an experiment.

Using interleaved transcranial magnetic stimulation (TMS) with functional MRI readouts from targeting multiple sites in sequence (Figure 1; red, blue TMS coils) can provide evidence for which cortical stimulation site evokes the better brain (region of interest or network) response (hypothetical fMRI BOLD responses red vs. blue). This feedback can then be used to decide on a subsequent treatment target individualized to each patient and brain response of interest (right side image). The tools already exist to apply this type of protocol but have not yet been attempted in a treatment study.

Conclusion

A great deal can be learned by pairing TMS with fMRI in affective disorders. We can obtain basic knowledge of how the disorder works, how individual patients with specific symptoms are best described, and how to more effectively treat patients with brain-based interventions. Combining TMS with fMRI is an excellent bridge between a treatment (rTMS) whose mechanisms are incompletely understood and that needs to be optimized and a measurement widely used to describe neuropsychiatric disorders but that has had little impact on improving patient outcomes. After all, rTMS is an explicitly brain based treatment and fMRI is explicitly a measure of brain function. Broadly, the study designs we outline here are applicable to other forms of imaging such as PET, EEG, and MR spectroscopy as well as to other forms of brain stimulation such as electrical stimulation and focused ultrasound. However, there is superior evidence for rTMS in treating affective disorders and for generating strong reproducible brain responses. In parallel, there is an exceptionally rich literature using fMRI to describe affective disorders. Therefore, the pairing of TMS with fMRI in this population has particularly solid footing that should be built upon by clinical researchers.

Funding Information

National Institute of Mental Health, National Institutes of Health USA (R01 MH120811; RF1 MH116920; R01 MH111886; U01-MH-109991; K01 MH121777; DP5-OD021352).

References

Aguirre GK (2007). Continuous carry-over designs for fMRI. Neuroimage, 35(4), 1480–1494. [PubMed: 17376705]

Allen EA, Pasley BN, Duong T, & Freeman RD (2007). Transcranial magnetic stimulation elicits coupled neural and hemodynamic consequences. Science, 317(5846), 1918–1921. doi:10.1126/science.1146426 [PubMed: 17901333]

Ashby FG (2019). Statistical analysis of fMRI data: MIT Press.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Balderston NL, Beydler EM, Roberts C, Deng ZD, Radman T, Lago T, … Grillon C (2020). Mechanistic link between right prefrontal cortical activity and anxious arousal revealed using transcranial magnetic stimulation in healthy subjects. Neuropsychopharmacology, 45(4), 694–702. doi:10.1038/s41386-019-0583-5 [PubMed: 31791039]

Balderston NL, Beydler EM, Roberts C, Deng ZD, Radman T, Luber B, … Grillon C (in press). A generalized workflow for conducting electric-field optimized fMRI-guided transcranial magnetic stimulation. . Nature Protocols.

Balslev D, Braet W, McAllister C, & Miall RC (2007). Inter-individual variability in optimal current direction for transcranial magnetic stimulation of the motor cortex. Journal of neuroscience methods, 162(1–2), 309–313. [PubMed: 17353054]

Bartko JJ (1966). The intraclass correlation coefficient as a measure of reliability. Psychological reports, 19(1), 3–11. [PubMed: 5942109]

Bartko JJ (1976). On various intraclass correlation reliability coefficients. Psychological bulletin, 83(5), 762.

Bassett DS, & Sporns O (2017). Network neuroscience. Nat Neurosci, 20(3), 353–364. [PubMed: 28230844]

Beer JC, Tustison NJ, Cook PA, Davatzikos C, Sheline YI, Shinohara RT, … Initiative, A. s. D. N. (2020). Longitudinal ComBat: A method for harmonizing longitudinal multi-scanner imaging data. Neuroimage, 220, 117129. [PubMed: 32640273]

Bestmann S, Baudewig J, Siebner HR, Rothwell JC, & Frahm J (2005). BOLD MRI responses to repetitive TMS over human dorsal premotor cortex. Neuroimage, 28(1), 22–29. [PubMed: 16002305]

Betzel RF, Avena-Koenigsberger A, Goñi J, He Y, De Reus MA, Griffa A, … Hagmann P (2016). Generative models of the human connectome. Neuroimage, 124, 1054–1064. [PubMed: 26427642]

Betzel RF, Gu S, Medaglia JD, Pasqualetti F, & Bassett DS (2016). Optimally controlling the human connectome: the role of network topology. Sci Rep, 6, 30770. [PubMed: 27468904]

Beynel L, Deng L, Crowell CA, Dannhauer M, Palmer H, Hilbig S, … Cabeza R (2020). Structural controllability predicts functional patterns and brain stimulation benefits associated with working memory. Journal of Neuroscience, 40(35), 6770–6778. [PubMed: 32690618]

Bijsterbosch J, Harrison SJ, Jbabdi S, Woolrich M, Beckmann C, Smith S, & Duff EP (2020). Challenges and future directions for representations of functional brain organization. Nat Neurosci, 1–12. [PubMed: 31844312]

Bohning DE, Shastri A, McConnell KA, Nahas Z, Lorberbaum JP, Roberts DR, … George MS (1999). A combined TMS/fMRI study of intensity-dependent TMS over motor cortex. Biol Psychiatry, 45(4), 385–394. doi:10.1016/s0006-3223(98)00368-0 [PubMed: 10071706]

Borckardt JJ, Walker J, Branham RK, Rydin-Gray S, Hunter C, Beeson H, … George MS (2008). Development and evaluation of a portable sham transcranial magnetic stimulation system. Brain Stimul, 1(1), 52–59. [PubMed: 19424444]

Bowring A, Telschow F, Schwartzman A, & Nichols TE (2019). Spatial confidence sets for raw effect size images. Neuroimage, 203, 116187. doi:10.1016/j.neuroimage.2019.116187 [PubMed: 31533067]

Bravo G, & Potvin L (1991). Estimating the reliability of continuous measures with Cronbach's alpha or the intraclass correlation coefficient: toward the integration of two traditions. Journal of clinical epidemiology, 44(4–5), 381–390. [PubMed: 2010781]

Brick JM, & Kalton G (1996). Handling missing data in survey research. Stat Methods Med Res, 5(3), 215–238. doi:10.1177/096228029600500302 [PubMed: 8931194]

Cattaneo Z, & Silvanto J (2008). Time course of the state-dependent effect of transcranial magnetic stimulation in the TMS-adaptation paradigm. Neuroscience letters, 443(2), 82–85. [PubMed: 18672027]

Chen AC, Oathes DJ, Chang C, Bradley T, Zhou ZW, Williams LM, … Etkin A (2013). Causal interactions between fronto-parietal central executive and default-mode networks in humans. Proc Natl Acad Sci U S A, 110(49), 19944–19949. doi:10.1073/pnas.1311772110 [PubMed: 24248372]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Cohen JD, Daw N, Engelhardt B, Hasson U, Li K, Niv Y, … Willke TL (2017). Computational approaches to fMRI analysis. Nat Neurosci, 20(3), 304–313. doi:10.1038/nn.4499 [PubMed: 28230848]

Cole MW, Braver TS, & Meiran N (2017). The task novelty paradox: Flexible control of inflexible neural pathways during rapid instructed task learning. Neuroscience & Biobehavioral Reviews, 81, 4–15. [PubMed: 28789810]

Cole MW, Repovš G, & Anticevic A (2014). The frontoparietal control system: a central role in mental health. The Neuroscientist, 20(6), 652–664. [PubMed: 24622818]

Corp DT, Bereznicki HG, Clark GM, Youssef GJ, Fried PJ, Jannati A, … Chung SW (2020). Large-scale analysis of interindividual variability in theta-burst stimulation data: Results from the 'Big TMS Data Collaboration'. Brain Stimul.

Dewey BE, Zhao C, Reinhold JC, Carass A, Fitzgerald KC, Sotirchos ES, … Calabresi PA (2019). DeepHarmony: a deep learning approach to contrast harmonization across scanner changes. Magnetic resonance imaging, 64, 160–170. [PubMed: 31301354]

Dixon ML, De La Vega A, Mills C, Andrews-Hanna J, Spreng RN, Cole MW, & Christoff K (2018). Heterogeneity within the frontoparietal control network and its relationship to the default and dorsal attention networks. Proceedings of the National Academy of Sciences, 115(7), E1598–E1607.

Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, … Etkin A (2017). Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nature medicine, 23(1), 28–38.

Dubois J, & Adolphs R (2016). Building a Science of Individual Differences from fMRI. Trends Cogn Sci, 20(6), 425–443. doi:10.1016/j.tics.2016.03.014 [PubMed: 27138646]

Dwan K, Li T, Altman DG, & Elbourne D (2019). CONSORT 2010 statement: extension to randomised crossover trials. bmj, 366, l4378. [PubMed: 31366597]

Etkin A, Prater K, Schatzberg A, Menon V, & Greicius M (2009). Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. Arch Gen Psychiatry, 66(12), 1361. [PubMed: 19996041]

Etkin A, & Wager TD (2007). Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry, 164(10), 1476–1488. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17898336 [PubMed: 17898336]

Fonzo GA, Goodkind MS, Oathes DJ, Zaiko YV, Harvey M, Peng KK, … Etkin A (2017). PTSD Psychotherapy Outcome Predicted by Brain Activation During Emotional Reactivity and Regulation. Am J Psychiatry, 174(12), 1163–1174. doi:10.1176/appi.ajp.2017.16091072 [PubMed: 28715908]

Fonzo GA, Goodkind MS, Oathes DJ, Zaiko YV, Harvey M, Peng KK, … Etkin A (2017). Selective Effects of Psychotherapy on Frontopolar Cortical Function in PTSD. Am J Psychiatry, 174(12), 1175–1184. doi:10.1176/appi.ajp.2017.16091073 [PubMed: 28715907]

Fortin J-P, Cullen N, Sheline YI, Taylor WD, Aselcioglu I, Cook PA, … McGrath PJ (2018). Harmonization of cortical thickness measurements across scanners and sites. Neuroimage, 167, 104–120. [PubMed: 29155184]

Fortin J-P, Parker D, Tunç B, Watanabe T, Elliott MA, Ruparel K, … Gur RE (2017). Harmonization of multi-site diffusion tensor imaging data. Neuroimage, 161, 149–170. [PubMed: 28826946]

Freedberg M, Reeves JA, Toader AC, Hermiller MS, Voss JL, & Wassermann EM (2019). Persistent Enhancement of Hippocampal Network Connectivity by Parietal rTMS Is Reproducible. eNeuro, 6(5). doi:10.1523/eneuro.0129-19.2019

Ganis G, Keenan JP, Kosslyn SM, & Pascual-Leone A (2000). Transcranial magnetic stimulation of primary motor cortex affects mental rotation. Cerebral Cortex, 10(2), 175–180. [PubMed: 10667985]

Geuter S, Lindquist MA, & Wager TD (2017). Fundamentals of functional neuroimaging.

Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, & Sporns O (2008). Mapping the structural core of human cerebral cortex. PLoS Biol, 6(7), e159. doi:10.1371/journal.pbio.0060159 [PubMed: 18597554]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Hamidi M, Slagter HA, Tononi G, & Postle BR (2009). Repetitive Transcranial Magnetic Stimulation Affects behavior by Biasing Endogenous Cortical Oscillations. Front Integr Neurosci, 3, 14. doi:10.3389/neuro.07.014.2009 [PubMed: 19587850]

Hassanzahraee M, Zoghi M, & Jaberzadeh S (2019). Longer Transcranial Magnetic Stimulation Intertrial Interval Increases Size, Reduces Variability, and Improves the Reliability of Motor Evoked Potentials. Brain Connectivity, 9(10), 770–776. [PubMed: 31744309]

Hawco C, Voineskos AN, Steeves JKE, Dickie EW, Viviano JD, Downar J, … Daskalakis ZJ (2018). Spread of activity following TMS is related to intrinsic resting connectivity to the salience network: A concurrent TMS-fMRI study. Cortex, 108, 160–172. doi:10.1016/j.cortex.2018.07.010 [PubMed: 30195825]

Houde F, Laroche S, Thivierge V, Martel M, Harvey M-P, Daigle F, … Leonard G (2018). Transcranial magnetic stimulation measures in the elderly: reliability, smallest detectable change and the potential influence of lifestyle habits. Frontiers in aging neuroscience, 10, 379. [PubMed: 30542278]

Huang YZ, Edwards MJ, Rounis E, Bhatia KP, & Rothwell JC (2005). Theta burst stimulation of the human motor cortex. Neuron, 45(2), 201–206. doi:10.1016/j.neuron.2004.12.033 [PubMed: 15664172]

Jonas E, & Kording KP (2017). Could a Neuroscientist Understand a Microprocessor? PLoS Comput Biol, 13(1), e1005268. doi:10.1371/journal.pcbi.1005268 [PubMed: 28081141]

Jung J, Bungert A, Bowtell R, & Jackson SR (2016). Vertex stimulation as a control site for transcranial magnetic stimulation: a concurrent TMS/fMRI study. Brain Stimul, 9(1), 58–64. [PubMed: 26508284]

Kaiser RH, Andrews-Hanna JR, Wager TD, & Pizzagalli DA (2015). Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. JAMA Psychiatry, 72(6), 603–611. [PubMed: 25785575]

Kammer T, Beck S, Thielscher A, Laubis-Herrmann U, & Topka H (2001). Motor thresholds in humans: a transcranial magnetic stimulation study comparing different pulse waveforms, current directions and stimulator types. Clinical Neurophysiology, 112(2), 250–258. [PubMed: 11165526]

Kebets V, Holmes AJ, Orban C, Tang S, Li J, Sun N, … Yeo BT (2019). Somatosensory-motor dysconnectivity spans multiple transdiagnostic dimensions of psychopathology. Biol Psychiatry, 86(10), 779–791. [PubMed: 31515054]

Keller CJ, Bickel S, Entz L, Ulbert I, Milham MP, Kelly C, & Mehta AD (2011). Intrinsic functional architecture predicts electrically evoked responses in the human brain. Proc Natl Acad Sci U S A, 108(25), 10308–10313. doi:10.1073/pnas.1019750108 [PubMed: 21636787]

Keller CJ, Bickel S, Honey CJ, Groppe DM, Entz L, Craddock RC, … Mehta AD (2013). Neurophysiological investigation of spontaneous correlated and anticorrelated fluctuations of the BOLD signal. J Neurosci, 33(15), 6333–6342. doi:10.1523/jneurosci.4837-12.2013 [PubMed: 23575832]

Kerwin LJ, Keller CJ, Wu W, Narayan M, & Etkin A (2018). Test-retest reliability of transcranial magnetic stimulation EEG evoked potentials. Brain Stimul, 11(3), 536–544. [PubMed: 29342443]

Komssi S, Kähkönen S, & Ilmoniemi RJ (2004). The effect of stimulus intensity on brain responses evoked by transcranial magnetic stimulation. Hum Brain Mapp, 21(3), 154–164. [PubMed: 14755835]

Kong R, Li J, Orban C, Sabuncu MR, Liu H, Schaefer A, … Yeo BTT (2019). Spatial Topography of Individual-Specific Cortical Networks Predicts Human Cognition, Personality, and Emotion. Cereb Cortex, 29(6), 2533–2551. doi:10.1093/cercor/bhy123 [PubMed: 29878084]

LeWinn KZ, Sheridan MA, Keyes KM, Hamilton A, & McLaughlin KA (2017). Sample composition alters associations between age and brain structure. Nat Commun, 8(1), 874. doi:10.1038/s41467-017-00908-7 [PubMed: 29026076]

Lindquist MA (2008). The Statistical Analysis of fMRI Data. Statistical Science, 23(4), 439–464. Retrieved from http://www.jstor.org/stable/20697652

Liston C, Chen AC, Zebley BD, Drysdale AT, Gordon R, Leuchter B, … Dubin MJ (2014). Default mode network mechanisms of transcranial magnetic stimulation in depression. Biol Psychiatry, 76(7), 517–526. doi:10.1016/j.biopsych.2014.01.023 [PubMed: 24629537]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Louis TA, Lavori PW, Bailar III JC, & Polansky M (1984). Crossover and self-controlled designs in clinical research. New England Journal of Medicine, 310(1), 24–31.

Luber B, Steffener J, Tucker A, Habeck C, Peterchev AV, Deng ZD, … Lisanby SH (2013). Extended remediation of sleep deprived-induced working memory deficits using fMRI-guided transcranial magnetic stimulation. Sleep, 36(6), 857–871. doi:10.5665/sleep.2712 [PubMed: 23729929]

Lynch CJ, Breeden AL, Gordon EM, Cherry JB, Turkeltaub PE, & Vaidya CJ (2019). Precision inhibitory stimulation of individual-specific cortical hubs disrupts information processing in humans. Cerebral Cortex, 29(9), 3912–3921. [PubMed: 30364937]

Marinescu IE, Lawlor PN, & Kording KP (2018). Quasi-experimental causality in neuroscience and behavioural research. Nat Hum Behav, 2(12), 891–898. doi:10.1038/s41562-018-0466-5 [PubMed: 30988445]

McTeague LM, Rosenberg BM, Lopez JW, Carreon DM, Huemer J, Jiang Y, … Etkin A (2020). Identification of common neural circuit disruptions in emotional processing across psychiatric disorders. American Journal of Psychiatry, 177(5), 411–421.

Medaglia JD, Harvey DY, White N, Kelkar A, Zimmerman J, Bassett DS, & Hamilton RH (2018). Network controllability in the inferior frontal gyrus relates to controlled language variability and susceptibility to TMS. Journal of Neuroscience, 38(28), 6399–6410. [PubMed: 29884739]

Mehler DM, Sokunbi MO, Habes I, Barawi K, Subramanian L, Range M, … Keedwell P (2018). Targeting the affective brain—a randomized controlled trial of real-time fMRI neurofeedback in patients with depression. Neuropsychopharmacology, 43(13), 2578–2585. [PubMed: 29967368]

Mejia AF, Yue Y, Bolin D, Lindgren F, & Lindquist MA (2020). A Bayesian general linear modeling approach to cortical surface fMRI data analysis. Journal of the American Statistical Association, 115(530), 501–520. [PubMed: 33060871]

Mill RD, Ito T, & Cole MW (2017). From connectome to cognition: The search for mechanism in human functional brain networks. Neuroimage, 160, 124–139. [PubMed: 28131891]

Modanwal G, Vellal A, Buda M, & Mazurowski MA (2020). MRI image harmonization using cycle-consistent generative adversarial network. Paper presented at the Medical Imaging 2020: Computer-Aided Diagnosis.

Mueller JK, Grigsby EM, Prevosto V, Petraglia FW 3rd, Rao H, Deng ZD, … Grill WM (2014). Simultaneous transcranial magnetic stimulation and single-neuron recording in alert non-human primates. Nat Neurosci, 17(8), 1130–1136. doi:10.1038/nn.3751 [PubMed: 24974797]

Nahas Z, Lomarev M, Roberts DR, Shastri A, Lorberbaum JP, Teneback C, … Bohning DE (2001). Unilateral left prefrontal transcranial magnetic stimulation (TMS) produces intensity-dependent bilateral effects as measured by interleaved BOLD fMRI. Biol Psychiatry, 50(9), 712–720. doi:S0006322301011994 [pii] [PubMed: 11704079]

Nandi A, Beard JR, & Galea S (2009). Epidemiologic heterogeneity of common mood and anxiety disorders over the lifecourse in the general population: a systematic review. BMC Psychiatry, 9, 31. doi:10.1186/1471-244x-9-31 [PubMed: 19486530]

Nettekoven C, Volz LJ, Kutscha M, Pool EM, Rehme AK, Eickhoff SB, … Grefkes C (2014). Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system. J Neurosci, 34(20), 6849–6859. doi:10.1523/jneurosci.4993-13.2014 [PubMed: 24828639]

Novaes MM, Palhano-Fontes F, Onias H, Andrade KC, Lobão-Soares B, Arruda-Sanchez T, … de Araujo DB (2020). Effects of Yoga Respiratory Practice (Bhastrika pranayama) on Anxiety, Affect, and Brain Functional Connectivity and Activity: A Randomized Controlled Trial. Frontiers in Psychiatry, 11, 467. [PubMed: 32528330]

O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, … Sackeim HA (2007). Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry, 62(11), 1208–1216. doi:10.1016/j.biopsych.2007.01.018 [PubMed: 17573044]

Oathes DJ, Bruce JM, & Nitschke JB (2008). Worry facilitates corticospinal motor response to transcranial magnetic stimulation. Depress Anxiety, 25(11), 969–976. doi:10.1002/da.20445 [PubMed: 18046733]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Oathes DJ, Zimmerman J, Duprat R, Cavdaroglu S, Scully M, Rosenberg B, … Shandler G (2018). Individualized non-invasive brain stimulation engages the subgenual anterior cingulate and amygdala. bioRxiv, 503441.

Oltedal L, Bartsch H, Sørhaug OJE, Kessler U, Abbott C, Dols A, … van Eijndhoven P (2017). The Global ECT-MRI Research Collaboration (GEMRIC): Establishing a multi-site investigation of the neural mechanisms underlying response to electroconvulsive therapy. NeuroImage: Clinical, 14, 422–432. [PubMed: 28275543]

Ozdemir RA, Tadayon E, Boucher P, Momi D, Karakhanyan KA, Fox MD, … Santarnecchi E (2020). Individualized perturbation of the human connectome reveals reproducible biomarkers of network dynamics relevant to cognition. Proceedings of the National Academy of Sciences, 117(14), 8115–8125.

Peters JC, Reithler J, de Graaf TA, Schuhmann T, Goebel R, & Sack AT (2020). Concurrent human TMS-EEG-fMRI enables monitoring of oscillatory brain state-dependent gating of cortico-subcortical network activity. Communications biology, 3.

Poldrack RA, Baker CI, Durnez J, Gorgolewski KJ, Matthews PM, Munafò MR, … Yarkoni T (2017). Scanning the horizon: towards transparent and reproducible neuroimaging research. Nature reviews neuroscience, 18(2), 115. [PubMed: 28053326]

Poldrack RA, Fletcher PC, Henson RN, Worsley KJ, Brett M, & Nichols TE (2008). Guidelines for reporting an fMRI study. Neuroimage, 40(2), 409–414. [PubMed: 18191585]

Pomponio R, Erus G, Habes M, Doshi J, Srinivasan D, Mamourian E, … Fan Y (2020). Harmonization of large MRI datasets for the analysis of brain imaging patterns throughout the lifespan. Neuroimage, 208, 116450. [PubMed: 31821869]

Power JD, Cohen AL, Nelson SM, Wig GS, Barnes KA, Church JA, … Petersen SE (2011). Functional network organization of the human brain. Neuron, 72(4), 665–678. doi:10.1016/j.neuron.2011.09.006 [PubMed: 22099467]

Reid AT, Headley DB, Mill RD, Sanchez-Romero R, Uddin LQ, Marinazzo D, … Biswal BB (2019). Advancing functional connectivity research from association to causation. Nat Neurosci, 22(11), 1751–1760. [PubMed: 31611705]

Reid AT, Headley DB, Mill RD, Sanchez-Romero R, Uddin LQ, Marinazzo D, … Cole MW (2019). Advancing functional connectivity research from association to causation. Nat Neurosci, 22(11), 1751–1760. doi:10.1038/s41593-019-0510-4 [PubMed: 31611705]

Riedel P, Heil M, Bender S, Dippel G, Korb FM, Smolka MN, & Marxen M (2019). Modulating functional connectivity between medial frontopolar cortex and amygdala by inhibitory and excitatory transcranial magnetic stimulation. Hum Brain Mapp, 40(15), 4301–4315. doi:10.1002/hbm.24703 [PubMed: 31268615]

Rolls ET, Cheng W, Gong W, Qiu J, Zhou C, Zhang J, … Cheng K (2019). Functional connectivity of the anterior cingulate cortex in depression and in health. Cerebral Cortex, 29(8), 3617–3630. [PubMed: 30418547]

Romero MC, Davare M, Armendariz M, & Janssen P (2019). Neural effects of transcranial magnetic stimulation at the single-cell level. Nature communications, 10(1), 1–11.

Rose NS, LaRocque JJ, Riggall AC, Gosseries O, Starrett MJ, Meyering EE, & Postle BR (2016). Reactivation of latent working memories with transcranial magnetic stimulation. Science, 354(6316), 1136–1139. doi:10.1126/science.aah7011 [PubMed: 27934762]

Ruff CC, Driver J, & Bestmann S (2009). Combining TMS and fMRI: from 'virtual lesions' to functional-network accounts of cognition. Cortex, 45(9), 1043–1049. doi:S0010–9452(08)00275-X [pii] 10.1016/j.cortex.2008.10.012 [doi] [PubMed: 19166996]

Sathappan AV, Luber BM, & Lisanby SH (2019). The dynamic duo: combining noninvasive brain stimulation with cognitive interventions. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 89, 347–360. [PubMed: 30312634]

Schaefer A, Kong R, Gordon EM, Laumann TO, Zuo XN, Holmes AJ, … Yeo BTT (2018). Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI. Cereb Cortex, 28(9), 3095–3114. doi:10.1093/cercor/bhx179 [PubMed: 28981612]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Schambra HM, Ogden RT, Martínez-Hernández I, Lin X, Chang YB, Rahman A, … Krakauer JW (2015). The reliability of repeated TMS measures in older adults and in patients with subacute and chronic stroke. Frontiers in cellular neuroscience, 9, 335. [PubMed: 26388729]

Schwarzkopf DS, Silvanto J, & Rees G (2011). Stochastic resonance effects reveal the neural mechanisms of transcranial magnetic stimulation. Journal of Neuroscience, 31(9), 3143–3147. [PubMed: 21368025]

Sheline YI, Barch DM, Price JL, Rundle MM, Vaishnavi SN, Snyder AZ, … Raichle ME (2009). The default mode network and self-referential processes in depression. Proceedings of the National Academy of Sciences, 106(6), 1942–1947.

Shou H, Eloyan A, Lee S, Zipunnikov V, Crainiceanu A, Nebel M, … Crainiceanu CM (2013). Quantifying the reliability of image replication studies: the image intraclass correlation coefficient (I2C2). Cognitive, Affective, & Behavioral Neuroscience, 13(4), 714–724.

Shoukri MM, Donner A, & El-Dali A (2013). Covariate-adjusted confidence interval for the intraclass correlation coefficient. Contemporary clinical trials, 36(1), 244–253. [PubMed: 23871746]

Siddiqi SH, Taylor SF, Cooke D, Pascual-Leone A, George MS, & Fox MD (2020). Distinct symptom-specific treatment targets for circuit-based neuromodulation. American Journal of Psychiatry, 177(5), 435–446.

Siegle GJ, Thompson WK, Collier A, Berman SR, Feldmiller J, Thase ME, & Friedman ES (2012). Toward clinically useful neuroimaging in depression treatment: prognostic utility of subgenual cingulate activity for determining depression outcome in cognitive therapy across studies, scanners, and patient characteristics. Arch Gen Psychiatry, 69(9), 913–924. [PubMed: 22945620]

Silvanto J, & Cattaneo Z (2014). State-dependent Transcranial Magnetic Stimulation (TMS) protocols. In Transcranial Magnetic Stimulation (pp. 153–176): Springer.

Silvanto J, & Muggleton NG (2008). Testing the validity of the TMS state-dependency approach: targeting functionally distinct motion-selective neural populations in visual areas V1/V2 and V5/MT+. Neuroimage, 40(4), 1841–1848. [PubMed: 18353682]

Stokes MG, Chambers CD, Gould IC, English T, McNaught E, McDonald O, & Mattingley JB (2007). Distance-adjusted motor threshold for transcranial magnetic stimulation. Clinical Neurophysiology, 118(7), 1617–1625. [PubMed: 17524764]

Struckmann W, Persson J, Weigl W, Gingnell M, & Bodén R (2020). Modulation of the prefrontal blood oxygenation response to intermittent theta-burst stimulation in depression: A sham-controlled study with functional near-infrared spectroscopy. World J Biol Psychiatry, 1–10. doi:10.1080/15622975.2020.1785007

Thielscher A, Antunes A, & Saturnino GB (2015). Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? Conf Proc IEEE Eng Med Biol Soc, 2015, 222–225. doi:10.1109/embc.2015.7318340

Thielscher A, Opitz A, & Windhoff M (2011). Impact of the gyral geometry on the electric field induced by transcranial magnetic stimulation. Neuroimage, 54(1), 234–243. doi:10.1016/j.neuroimage.2010.07.061 [PubMed: 20682353]

Trivedi MH, McGrath PJ, Fava M, Parsey RV, Kurian BT, Phillips ML, … Toups M (2016). Establishing moderators and biosignatures of antidepressant response in clinical care (EMBARC): rationale and design. J Psychiatr Res, 78, 11–23. [PubMed: 27038550]

Tye KM, Prakash R, Kim SY, Fenno LE, Grosenick L, Zarabi H, … Deisseroth K (2011). Amygdala circuitry mediating reversible and bidirectional control of anxiety. Nature, 471(7338), 358–362. doi:10.1038/nature09820 [PubMed: 21389985]

Vaseghi B, Zoghi M, & Jaberzadeh S (2015). Inter-pulse interval affects the size of single-pulse TMS-induced motor evoked potentials: a reliability study. Basic and Clinical Neuroscience, 6(1), 44. [PubMed: 27504156]

Vink JJT, Mandija S, Petrov PI, van den Berg CAT, Sommer IEC, & Neggers SFW (2018). A novel concurrent TMS-fMRI method to reveal propagation patterns of prefrontal magnetic brain stimulation. Hum Brain Mapp, 39(11), 4580–4592. doi:10.1002/hbm.24307 [PubMed: 30156743]

Wang J, Zuo X, & He Y (2010). Graph-based network analysis of resting-state functional MRI. Front Syst Neurosci, 4, 16. [PubMed: 20589099]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Williams LM (2016). Precision psychiatry: a neural circuit taxonomy for depression and anxiety. Lancet Psychiatry, 3(5), 472–480. doi:10.1016/s2215-0366(15)00579-9 [PubMed: 27150382]

Williams LM (2017). Defining biotypes for depression and anxiety based on large-scale circuit dysfunction: a theoretical review of the evidence and future directions for clinical translation. Depress Anxiety, 34(1), 9–24. doi:10.1002/da.22556 [PubMed: 27653321]

Wrobel J, Martin M, Bakshi R, Calabresi P, Elliot M, Roalf D, … Nair G (2020). Intensity warping for multisite MRI harmonization. Neuroimage, 117242. [PubMed: 32798678]

Xia CH, Ma Z, Ciric R, Gu S, Betzel RF, Kaczkurkin AN, … Satterthwaite TD (2018). Linked dimensions of psychopathology and connectivity in functional brain networks. Nat Commun, 9(1), 3003. doi:10.1038/s41467-018-05317-y [PubMed: 30068943]

Yu M, Linn KA, Cook PA, Phillips ML, McInnis M, Fava M, … Sheline YI (2018). Statistical harmonization corrects site effects in functional connectivity measurements from multi-site fMRI data. Hum Brain Mapp, 39(11), 4213–4227. [PubMed: 29962049]

Zhu AH, Moyer DC, Nir TM, Thompson PM, & Jahanshad N (2019). Challenges and opportunities in dMRI data harmonization. Paper presented at the International Conference on Medical Image Computing and Computer-Assisted Intervention.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Control conditions are critical to interpretability of TMS effects on brain or behavior

TMS stimulates nerves and muscles in the scalp robustly given their proximity to the TMS coil. Acoustical noise and mechanical vibration of the coil as it discharges are also significant indicators to a participant that verum (real, non-sham) stimulation has been administered. Given that sham stimulation is supposed to control for these factors, it may not be ideally effective to utilize spacers, shields or other impediments to dampen TMS current to the scalp. Nor is sham effective if the stimulator output is set to a lower amplitude which participants can reasonably detect as falling below the full stimulation level. Instead, two primary strategies for controlling non-specific TMS effects include: 1) electrical stimulation of the scalp (sham control) or 2) stimulating a 2nd cortical location that can be justified as an appropriate control site. Electrical stimulation of the scalp can be set to a level to mimic the sensation of TMS (Borckardt et al., 2008). Unfortunately, there is no commercial sham TMS device for the MRI environment. Therefore, we stimulate additional brain areas not expected to affect the brain network or pathway that is the focus of our primary stimulation site. For studying affective disorders, the motor cortex may not be ideal for this given its connections with subcortical targets implicated in these disorders and connectivity abnormalities across multiple disorders (A Etkin, Prater, Schatzberg, Menon, & Greicius, 2009; Kebets et al., 2019). Another common control site in TMS studies is the scalp vertex (Cz). Vertex stimulation primarily deactivates the DMN which is an expected result of non-specific sensory TMS effects (Jung, Bungert, Bowtell, & Jackson, 2016). Other strategies for choosing control sites depend on how the primary site was chosen. For example, a site chosen for high positive resting state connectivity could be contrasted with a site with negative or minimal connectivity. Similarly, a site with high task activation could be contrasted with a site showing minimal activation.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

TMS effects are state dependent

The neural and behavioral effects of TMS are not solely determined by how the stimulation is delivered, but instead by some combination of these parameters and the activity levels of targeted neuronal populations themselves (Sathappan, Luber, & Lisanby, 2019; Silvanto & Cattaneo, 2014). Such 'state-dependency' encompasses many factors that likely contribute to behavioral effects of TMS such as attention, timing, and psychiatric conditions (Silvanto & Muggleton, 2008). When experimentally-manipulated sensory brain states, such as adaptation (sustained prior exposure to a stimulus decreases future response to stimulus) are paired with single pulses of TMS, the adaptation effect is reversed (Cattaneo & Silvanto, 2008). The underlying mechanism of these sensory effects may be stochastic resonance, whereby TMS acts to boost otherwise subthreshold neuronal signals above a detection threshold (Schwarzkopf, Silvanto, & Rees, 2011). However, state-dependence is not only limited to perceptual experiments. TMS-state-dependence interactions are observed in sleep-deprivation (TMS eliminates working memory deficits in sleep-deprived subjects), and differing emotional (worry increases TMS evoked motor responses), and cognitive states (TMS of the primary motor cortex disrupts mental rotation) (Ganis, Keenan, Kosslyn, & Pascual-Leone, 2000; Luber et al., 2013; D. J. Oathes, Bruce, & Nitschke, 2008). A growing body of evidence outlines a role for neural rhythms in state-dependence as well. Pre-stimulation alpha power influences TMS-evoked BOLD response (Peters et al., 2020) and TMS-evoked neuronal oscillatory activity has been correlated with individual differences in cognitive ability (Ozdemir et al., 2020), for example.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

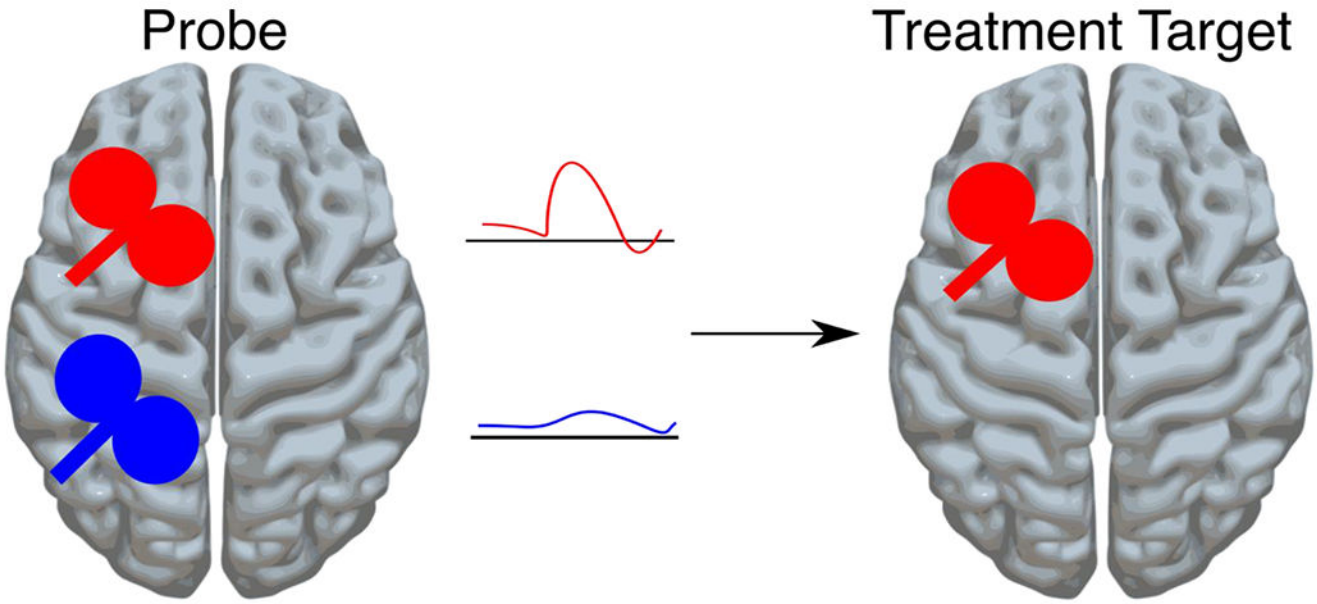


Figure 1.
A hypothesized schematic wherein transcranial magnetic stimulation (TMS) is applied to multiple possible sites (red, blue coils) and the fMRI evoked response (plots) are used to determine a treatment target (right side, red coil)