Supplemental Information

Methodological considerations for TMS

There are many methodological considerations when including TMS in research studies to investigate neocortical function and develop biomarkers of disease and disease progression. These include technical aspects of TMS, cohort selection and confounding factors, and subject safety.

Technical aspects of TMS

TMS paradigms are dependent on many technical parameters (1). The combination of the stimulating coil's geometry and orientation and the direction of current flow determine the dosage of the TMS pulse, the distribution of the magnetic field, the subsequently induced electric field, and the depolarization function (i.e., the efficacy of TMS) (2). The inductance of the coil determines the width of each TMS pulse, and pulse width corresponds to different physiological actions. Field strength decays as a function of distance. Depending on pulse shape (monophasic or incompletely balanced multiphasic pulses), the induced current may have a directionality that is sensitive to coil orientation. In such instances, rotation of the coil on the scalp, despite targeting the same brain region, can induce differential effects since different neural elements (depending on their orientation) will be depolarized. The geometry of the coil (e.g., circular versus figure-of-eight, flat versus cone-shaped) also alters the distribution (i.e., focality) of the induced magnetic and resulting electric fields, and the depth of penetrance of the generated field. A guiding principle in coil geometry selection is that there is a trade-off between focality and depth of penetrance, that is, the more focal the stimulation, the less penetrant the magnetic field. The TMS device also affects dosing, as devices may have different parameters such as pulse width, amplitude, and frequency. Commercially available TMS devices have pre-

specified pulse types with specific shape, directionality, and polarity. The pulses can be given in biphasic or monophasic trains, each of which has differential effects on cortical function. For instance, monophasic relative to biphasic trains are more efficient in inducing lasting intracortical inhibition. With current technology, most TMS devices only produce sine waves. Thus, in research investigations, a specified TMS device (e.g., producing monophasic trains) and coil type (e.g., figure-of-eight coil) should be selected carefully, so that they are optimal for the planned methodological experiments.

Targeting the stimulation site can be performed with a variety of techniques, such as the hand-held technique (3), the 10-20 International EEG system (4), or neuronavigational systems (e.g., guided by anatomical or functional data, or frameless stereotaxy such as Talairach coordinates) (5, 6). The hand-held technique is commonly used. For instance, targeting the dorsolateral prefrontal cortex (DLPFC) involves locating an ideal spot on the motor cortex to produce a motor evoked potential (MEP) on the contralateral hand muscle of interest; once the ideal spot is identified, the investigator then locates the DLPFC by stimulating a spot 5 to 6 centimeters (cm) anterior to the motor cortex 'hotspot'. However, this method can be precarious as it does not take into account interindividual differences in head size and anatomy or interexpert variability (7-9). To correct the hand-held technique, the 10-20 International EEG system can be used as it scales to head size. In either case, such methods fail to monitor, online and trial-by-trial, the consistency of the brain area targeted, and, given the various degrees of freedom involved (e.g., roll, pitch, yaw, etc.), it is difficult to achieve consistency in the targeted brain region within and across TMS sessions (5). Such lack of specificity introduces variability in the effects of TMS. Neuronavigation methods that utilize the individual's magnetic resonance imaging (MRI), for instance, can be used to reliably locate the stimulation site through computer-guided assistance and, thus, assure accuracy and precision within and across TMS sessions. Sack *et al.* (6) systematically studied different coil positioning methods to examine the acute effects of TMS on a specific behavioral task associated with a specific brain

region and found a low effect size (d = 0.34) for the hand-held technique and large effect sizes for MRI- (d = 0.82) and functional MRI (fMRI)-guided (d = 1.13) site stimulation methods. Furthermore, Fitzgerald *et al.* (10) found a better outcome in the MRI-targeted group compared with the standard localization group at 4 weeks in a randomized trial of rTMS for the treatment of major depression. Thus, brain targeting techniques can substantially impact the outcome of TMS paradigms, inasmuch as it would be prudent to employ neuronavigation methods to ensure reliable stimulation of the targeted cortical area during single and repeated TMS sessions (Figure 2).

Cohort selection and confounding factors

The study cohort can attenuate the effects of TMS due to the presence of psychiatric pathology. As the electric field generated from the TMS coil is dependent upon the medium of induction, psychiatric pathology could result in cortical atrophy or morphological changes which can alter the induced magnetic and electric fields (1, 11). In schizophrenia, several studies have demonstrated progressive structural brain changes [for review, (12)]. For instance, gray matter reductions, shown to be more pronounced in the prefrontal and temporal lobes (13), were longitudinally traced, along with expansion of white matter volumes in frontal, parietal, and isolated temporal lobe regions [e.g., (14)]. However, some investigators have performed volumetric analysis of gray matter underlying the TMS coil between schizophrenia patients and comparison healthy controls to exclude this potential confounder (15).

A critical factor to consider, particularly when studying schizophrenia patients, is the use of psychotropic medications to treat psychiatric symptoms. These medications can modify the effects of TMS and thus affect the reliability of TMS findings. Moreover, TMS-induced neurotransmitter release at the synapse and transsynaptic action can be affected by the introduction of psychotropic drugs. For example, Soubasi *et al.* (16) showed that the therapeutic regimen conditioned the alterations in neuronal excitability in schizophrenia patients. Pascual-

Leone *et al.* (17) showed that intracortical inhibition and facilitation measured with paired-pulse TMS are affected by neuroleptic medications and remain altered in patients who have been off medication for years. Observed TMS effects can thus be attributable to schizophrenia, antipsychotic medication (present or even past), and/or the interaction between these factors. Psychotropic medication can also increase safety concerns if they lower threshold for seizures.

Another methodological consideration regards the introduction of confounders produced by auditory clicking and tactile sensation on the scalp as each can activate the brain. To control for these sensory confounders, different techniques have been introduced and proposed as sham-stimulation conditions. These techniques include tilting of the stimulating coil, inserting a metal shield in the coil, cancelling the magnetic field, and using sham coils capable of producing similar sensory sensations (18). However, despite all these efforts, none of the available systems truly mask both examiners and participants, particularly those who experience TMS more than once. More sophisticated, technological solutions for sham TMS are needed and are being explored (19).

Subject safety

Investigations including TMS paradigms in their experimental design should incorporate and adhere to the safety guidelines published by Wasserman (20) and updated by the Safety of TMS Consensus Group (21) in order to ensure subject safety. The main adverse effects produced by TMS include headache and mild scalp pain at the site of stimulation, which can be treated with over-the-counter analgesics. Though TMS is a relatively safe technique, particularly when administered at low intensities with stimulating coils that do not penetrate to subcortical structures, TMS can produce a seizure. Since the introduction of safety guidelines (20), there have been only a few reported cases of such adverse effects. A useful measure to include in any investigation that will recruit human participants and employ TMS paradigms is the Transcranial Magnetic Stimulation Adult Safety Screen (TASS), which will help to minimize the

inclusion of participants for whom TMS may have greater risk for seizures and other adverse events (22).

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