Meeting Report: Transcranial Magnetic Stimulation and Studies of Human Cognition.

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A James S. McDonnell Foundation workshop[1] examined the role of TMS in studies of human cognition. A summary of the workshop presentations, discussion, and the recommendations appear below[2]. A selected reference list is provided at the end of the summary.

Cognitive neuroscience studies how the physical structure of the brain subserves the cognitive processes of the mind. Such studies with humans are hampered by technical difficulties. One classic approach to human subject studies has been observing the cognitive performance of individuals who have suffered focal brain injuries. More recently, non-invasive brain monitoring has allowed investigation of how human cognitive performance is linked with neural substrates in intact human subjects. A number of such non-invasive brain monitoring tools have been developed, each with its own individual strengths and weaknesses. EEG and MEG detect neural activity during cognitive performance with good temporal resolution but are less useful for identifying precisely where in the brain the neural activity is occurring. PET and fMRI, monitoring signals correlated with hemodynamic and metabolic indicators of neuronal activity, provide good spatial identification of brain areas involved in the performance of cognitive tasks, but are limited

[1] The agenda and list of participants is available on the McDonnell Foundation website www.jsmf.org.
[2] The authors of this summary take full responsibilty for the details provided. This summary does not provide a consensus statement approved by workshop participants.

in their temporal resolution. Increasingly, cognitive neuroscientists offset the technical limitations of each by using these technologies in combination.

Over the last several years, cognitive neuroscientists have added a new tool to their box - transcranial magnetic stimulation (TMS). Until recently, TMS was used principally by neurophysiologists to stimulate neurons in the primary motor cortex or in peripheral nerves. Its value lay principally in removing the requirement that subjects perform voluntary tasks. In cognitive neuroscience, TMS is used for broader purposes.

TMS requires a coil producing a pulsed current. This current generates a pulsed magnetic field that causes neurons in a specific volume of brain under the coil to depolarize synchronously. When the pulsed magnetic field is applied to a part of the brain thought to be necessary for the performance of a cognitive task, the resulting depolarization interferes with the ability of the subject to perform the task. In principle then TMS provides the cognitive neuroscientist with the capability to induce highly specific, temporally and spatially precise interruptions in cognitive processing - what some researchers call "virtual lesions".

Creating temporary lesions is not the only application of TMS technology relevant to cognitive neuroscience. In other laboratories, TMS is used to study cortical plasticity and the effects of drugs, hormones and disease on cortical excitability. Clinical scientists interested in depression and other mental illnesses use TMS as a form of therapy similar to electro-convulsive shock therapy.

As with the introduction of any new technique to a field, the use of TMS in cognitive neuroscience is not without controversy. The technical use of TMS of most interest to cognitive neuroscientists involves the application of multiple pulses, or what is called repetitive TMS (rTMS). Issues of subject safety and the mechanism of action by which rTMS effects neuronal

functions remain to be resolved. Repetitive TMS stimulation has and could trigger seizures in susceptible subjects. Studies also suggest that TMS could induce long-term cognitive effects by altering synaptic activity or neurotransmitter balance. The TMS response threshold also varies among subjects, requiring careful data interpretation. While early studies with rTMS have had the positive effect of encouraging researchers to think about the cellular mechanisms accounting for individual responses, individual differences complicate the establishment of experimental guidelines.

As for mechanism of action, it is generally agreed that the mechanism involves the synchronous depolarization of neurons followed by a period of inhibition. The specific actions of the TMS pulse on individual classes of neurons and the duration of the inhibition period are less well characterized. The specific currents induced by the TMS pulse depend heavily on the distribution of conductivity in the brain and on the coil position. These dependencies have not been calculated in detail.

Anticipating an increased use of TMS in cognitive neuroscience research, the McDonnell Foundation brought together leading cognitive researchers, biophysicists, neurophysiologists, and others with expertise using TMS, to discuss its safety, mechanisms of action, and potential contributions to studies linking brain and cognition. The main points raised during the workshop are described below, organized under topical questions.

How does TMS alter brain activity?

Eric Wasserman (NIH) and John Rothwell (University of Oxford) each provided summaries of how magnetic stimulation is thought to effect neuronal function. In a TMS experiment, a metal coil is placed above the cortical region of interest. The coil is usually circular or figure-eight in

design. Delivering a strong electric current through the coil for brief durations induces a magnetic field. The geometry of the coil and the amplitude of the current input determine the field strength and its distribution. The magnetic field rapidly falls off with distance from the coil center (for a circular coil the field falls off as the third power of the coil's radius). This rapid decrease in field strength limits TMS to the study of superficial cortical regions. Following Faraday' s law, the rapidly changing magnetic field induces an electric field in the brain. A common misconception is that the strength of the electric field is proportional to the magnetic field strength. Actually, it is proportional to the magnetic field flux. This distinction is quite important for interpreting TMS signals. For example, with a circular coil the magnetic field is strongest along the axis through the center of the coil, but the induced current is zero. In addition, as discussed below, the electrical conductivity of the brain and surrounding structures may strongly influence the induced current distribution.

The electric field from the TMS pulse induces ionic currents in the brain which lower the potential of neuronal membranes and initiates a depolarization. The probability of a neuron depolarizing in response to a TMS pulse train depends on the state of the neuronal membrane potential, the orientation of the neuron relative to the induced current, and the type of neuron. It is believed the depolarization takes place primarily in the axons of projecting pyramidal cells. It is controversial whether the depolarization is caused by a direct effect of the induced current on the cell body or whether it is an indirect effect of the current on the activity of nearby inhibitory interneurons. The synchronous depolarization of neurons exposed to the current is followed by a period of inhibition. The inhibition period is believed to be mediated by GABAergic synapses. Inhibition is strongly enhanced by drugs that increase the sensitivity of the GABA-A receptor or increase GABA release. The mechanisms by which the strength of GABAergic synapses are

enhanced by TMS are not fully known, but it is believed to reflect intracortical connectivities. Longer range connectivities (e.g. cortico-thalamic) may also influence synaptic strength after the TMS pulse train. Following the inhibitory period, there is a facilitory period in which the current required to induce a depolarization is decreased. While further research is needed to define the neuronal mechanisms, the observed effect is a disruption of normal neuronal firing over a variable time period. Since the effect of TMS is a physiological and biochemical disruption of normal neuronal activity, we suggest that use of the term "virtual lesion" is a bit misleading.

Jon Kaas (Vanderbilt University) asked how TMS stimulation effects synaptic weights. If TMS alters synaptic weighting it would be useful for exploring synaptic plasticity. Tomas Paus (Montreal Neurological Institute) explained that there is a short-term time dependent effect on synaptic weights. When using paired pulses, the cumulative effect can be either facilitative or inhibitory, depending on the time separating the two pulses. In response to queries about the temporal aspect of TMS effects on synaptic weights, Peter Fox (U. Texas Health Sciences Center) reported that TMS-induced LTP can last several hours, while LDP can last as long as 24 hours.

Several meeting participants also described the effect of TMS as causing an increase in noise in a specific volume of brain tissue. Following this observation, Steve Hanson (Rutgers University) initiated a lively discussion when he suggested that the effects of TMS were being given rather mechanistically vague characterizations. As Hanson pointed out, it would be difficult to translate "synchrony" or "increased noise" into precise terms that made sense from a computational perspective.

What can we learn about the use of TMS from animal studies?

The majority of information on the mechanism of TMS has come from studies of the human motor cortex. The limitations on invasive studies in humans leave many questions unanswered about how TMS effects neuronal function over the short- and long-term and whether different subpopulations of neurons might be more or less susceptible to the effects of the electromagnetic pulses. Holly Lissanby (Columbia University) explained that experiments with small animals are difficult because there are technical limits on building RF coils of the size required to stimulate distinct brain regions. For circular coils at an equivalent distance (fraction of a coil radius) from the brain region, the efficiency of a small coil relative to a larger coil in inducing electrical fields in the brain decreases as the relative radius of the coils (a 2x larger coil is 2x more efficient). Similar relationships hold for other coil geometries. Therefore, smaller coils require larger currents to drive them, which in turn create mechanical stability and heating problems.

Despite the limitations, animal studies are being used to investigate the effects of TMS on the brain. The data suggest that TMS can result in changes mimicking the effects of both long term potentiation (LTP) and long term depression (LTD). TMS does induce some changes in neurotransmitter systems; more studies are needed to tease out what the acute and/or chronic effects of these changes might be. There is some evidence that chronic application of TMS can lead to dendritic sprouting and an increase in the number of synapses. This, of course, raises the issue of whether TMS should be considered a "non-invasive" monitoring technology at all. Some animal researchers, interested in obtaining more precise localization, are beginning to implant electrodes in the brain, rather than stimulating the brain with surface TMS coils. The importance of knowing how TMS changes neuronal function outweigh the difficulties of animal experiments and such studies should be an integral part of any TMS laboratory.

Emilio Bizzi (MIT) emphasized that TMS studies should be pursued with primates where it should be possible to partner TMS with more invasive monitoring techniques such as single cell recording. These studies would allow more precise answers to questions about the neurochemical and neurophysiological effects of TMS. Bizzi asked if it was possible to build miniaturized or implantable coils. Several participants felt that implanted coils would be unsafe due to the large electric currents required in the coil. Such currents would result in tissue heating and mechanical vibration. However, no one objected to the possibility of improving the design of miniaturized external coils that would be suitable for primate and other animal applications.

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What determines the spatial and temporal resolution of TMS effects in human subjects?

Fairly wide ranges of opinions were offered about the size of the brain region affected by TMS. Some reports claim millimeter resolution, while others suggest that the practical resolution might be several centimeters at best. The spatial localization of TMS depends upon the distribution of the induced ionic current in the brain. These currents in turn depend upon the spatial distribution of the pulsed magnetic field from the TMS coil, the strength and waveform of the pulse, and the geometry and conductive properties of the brain. Another source of variability in the spatial resolution of TMS is the secondary effects on neurons connected to the neurons in the primary site of the TMS stimulation. Rather than being an unwanted complication in the interpretation of TMS, this distant action effect could be exploited for studying connectivity mapping. Combined TMS/fMRI or TMS/EEG studies were suggested as a way to further develop this line of research.

The strong spatial dependence of the induced electric field and its rapid decrease in intensity with the distance away from the coil, together with the influence of coil geometry, also make it essential for experimenters to carefully control these variables. Mark George (Medical College of

South Carolina) provided results from MRI which showing that controlling the distance between the TMS coil and the cortex yielded more consistent TMS results. George also warned that researchers must pay particular attention to critical variables like the coil-cortex distance when using TMS to study special subject populations including children, the elderly (where there could be some cortical atrophy leading to a changes in conductivity), and patients with diseases states that might effect cortical volume.

Peter Fox, whose laboratory uses a robotic arm to achieve consistent coil placement, made a strong case as to why researchers should describe coil specifications and coil placement in detail. For example, the current distribution and orientation from a figure eight coil is considerably different than those of a circular coil. The extreme case is that in a circular coil induces no current along the center axis of the coil, while in a figure-eight coil current induction is highest along the center axis. It was generally agreed that standardization of TMS procedures would be of great importance in reconciling the sometimes conflicting results that are emerging from different laboratories. Douglas Rothman (Yale) pointed out that programs for performing detailed calculations of currents induced by pulsed magnetic fields in non-uniform conductive media such as the brain are available from MRI research where similar problems arise.

It is important for researchers to also think carefully about research questions and subject populations for which TMS may not be suitable. TMS coils, as currently designed, are best suited for studies where the region of interest is in more superficial cortex. It is not possible to stimulate deep cortical neurons or subcortical nuclei without depolarizing the more superficial neurons. Once more sophisticated methods are used to calculate the induced current distribution, it may be possible to design TMS coils which stimulate deeper brain regions. There are also needs for studies that look at whether it is primarily the neuronal cell body or the axon that is affected by the induced

current. Studies are needed as well on the cellular parameters that account for possible changes of synaptic weighting. The brain's irregular surface raises the question of whether TMS would differentially effect neurons in the sulci or gyri.

Wasserman emphasized the importance of carefully considering spatial and temporal factors with a telling example of how a TMS study on a patient with a cerebral infarction could have led the investigators to mistakenly conclude that a cognitive function had migrated to another brain region. In this patient, stimulating the left parietal/temporal/ frontal regions interfered with picture naming, while in control subjects no interference was found. Wasserman's explanation for the result was that the CSF in the infarcted brain region acted as a high conductivity pathway, shunting current to regions of the brain that should not have responded to the TMS stimulus considering coil placement. Had the anatomical alterations of this subject's brain not been considered, the study could have led to a conclusion that the function had shifted location in this patient.

The discussion of the temporal resolution of the "virtual lesion" induced by TMS also provoked some controversy. When used for creating "virtual lesions", TMS is often applied repeatedly within a relatively short time period. Repetitive pulses are required to obtain multiple measures of altered function that allow statistical analysis. The danger of this approach is, as discussed above, that the TMS pulses may have an accumulating effect on cognitive function. Holly Lissanby provided examples of such accumulating effects. In animal studies, repeated applications of TMS resulted in dendritic sprouting in the rat cerebral cortex. Several discussants pointed out that the potential usefulness of treating depression and other disorders with TMS depends on its ability to cause long-lasting and cumulative effects on humans. Care must be taken to define the boundaries determining transient effects from chronic. Again, it is imperative that animal experiments and studies combining TMS with other techniques measuring correlates of

neuronal activity (e.g. fMRI and EEG) be carried out to determine precisely TMS's spatial and temporal dimensions under varied conditions.

What can TMS be expected to uniquely contribute to studies of human cognition?

If TMS can reliably create transient, if not true "virtual" lesions, it could be used to determine if the neuronal activity in particular brain regions are necessary for performing a cognitive task. Unlike studying subjects whose brain lesions result from disease or injury, the locations of the lesions created by TMS can be selected to test specific theories of cognitive function, assuming we are able to further our understanding of the spatial and temporal dynamics. The generally short duration of the TMS experiment should prevent the confounding of results by structural re-organization or other compensatory changes, such as developing new strategies, that could occur with long-existing brain injuries. If so, TMS studies could play a complementary role to PET and fMRI studies. PET and fMRI can monitor whether or not a brain area changes the level of neuronal activity during the performance of a cognitive task, but not if the activity in any particular brain area is absolutely required by the task.

TMS could also be used to map connectivity among different brain areas since TMS stimulation can reasonably be expected to exert effects on regions not directly stimulated, but functionally connected to the brain tissue stimulated by the induced current. The ability to map connections could wind up being a major strength of TMS but adds complications to determinations of spatial selectivity. Mark George's' lab has reported that TMS pulses can effect tissue not directly under the coil; application of the TMS pulse to the motor cortex can result in inhibition of activity in the contra-lateral motor cortex. Peter Fox also reported that there is some spread of depolarization across the cerebral hemispheres. It will be important to determine

whether distinct brain regions altered by the TMS pulse are effected as a result of functional connectivity or non-specific spread of current. Interpretation of TMS data requires careful analysis of the duration and number of pulse applications, cumulative exposure, coil geometry and orientation relative to the cortex, and distribution of neuronal populations distribution, as well as long distance connectivities.

When designing experiments, researchers will need to grabble with the lack of adequate control conditions for subjects participating in TMS studies. The coil makes an audible "click" when turned on and the stimulation of superficial nerves often causes involuntary contractions of muscles in the scalp, face, and neck. The side effects are very distracting and disturbing to subjects.

An area where TMS may uniquely contribute to cognitive neuroscience is in attempts to understand the biological basis of learning. PET studies, such as those published by Steve Petersen and his colleagues at Washington University, show that the brain region activated while a subject learns a novel task need not be the same brain regions activated when the subject perform the task after it has becomes over-learned or "automatic". Walsh reported findings from his laboratory showing that TMS stimulation of an area involved in acquiring a skill does not disrupt a subject's skilled performance. Rather than using TMS to create "virtual" lesions, it has been used as a read-out pulse to assess cortical plasticity in motor-learning tasks. Studies by Leonardo Cohen and coworkers using neuroleptics have shown that TMS might actually influence cortical plasticity by modulating the activity of inhibitory GABAergic synapses. Cohen’s studies raise interesting questions about the classic model of learning requiring modulation of excitatory glutamatergic synapses.

What studies need to be done before TMS is widely applied for studying human cognition?

In addition to basic work on safety, there are considerable limitations in our understanding of the spatial and temporal resolution of the TMS effect as well as its effects on the underlying neuronal populations. Stephen Kosslyn (Harvard) stated that the present uncertainties of TMS should not necessarily limit its use studying human cognitive processes. Kosslyn reminded the participants that despite the many unanswered questions concerning the fundamental neurochemical and neurophysiological mechanisms tapped in fMRI experiments, particularly the relationship between the observable signal and the neuronal processes reflected in such signal changes, fMRI studies have provided valuable information about brain structure-function relationships[3]. Functional MRI may not be the best analogy because TMS is not an external brain imaging or brain "sensing" device. The power of TMS as an experimental tool derives from its ability to interfere with or alter neuronal activity. Therefore, mechanistic uncertainties about the effects of TMS on neuronal function seriously hamper the ability to resolve interpretation of studies, particularly when there is discordance between the findings obtained via TMS versus other methods. An example discussed at length was the interpretation of studies in which fMRI experiments implicated a particular brain region as activated during the performance of a cognitive task, but where TMS stimulation of that brain region does not interfere with task performance. One interpretation proposed earlier in the session was that the lack of interference indicated the region was not involved in task performance. Several participants pointed out that due to the uncertainties about mechanism of action the lack of TMS effect was equally well explained by supposing that the class of neurons in the region critical for the task was not effectively depolarized by the TMS pulses. Several discussants argued that such counter examples were naïve since they

[3] A prior McDonnell Foundation workshop discussed unanswered questions concerning techniques measuring cerebral blood flow and metabolism. See *New Approaches to Functional Neuroenergetics*, J. Cog. Neuro. 11:4, 467-471, 1999.

discounted the vast wealth of knowledge of cognitive processes obtained by conventional cognitive psychology in combination with lesion studies prior to the development of imaging methods. This knowledge provides a gold standard for evaluating the validity of a TMS or fMRI result. Those present who routinely use fMRI for their research added that without these constraints it would be impossible to localize cognitive processes with fMRI, since large regions of the brain are invariably activated. This argument was criticized for its circularity - that due to the uncertainties about the technique results from TMS are only accepted when they agree with the hypothesis. It was further suggested that this way of thinking limits the ability of TMS and other modern functional mapping techniques to make novel contributions to our understanding of cognitive processing.

Distinct from the issue of the electrical current limits that should be placed on human TMS studies, participants generally agreed that studies to better define the spatial, temporal and neuronal resolution of the method, as well as improvements in TMS technology, would greatly benefit the application of this technique.

Safety issues in rTMS - how virtual is the 'virtual lesion'?

Although sometimes called a noninvasive method because it involves no direct mechanical interaction with brain tissue rTMS must be treated as an invasive and potentially dangerous technique since it interferes with brain electrical activity and synaptic weightings (as would a pharmacological agent). Eric Wasserman summarized the technical and safety aspects of rTMS as determined at an NIH -sponsored consensus conference (see reference 3). The major known risks of rTMS are induction of seizures, headaches, short to medium term (several hours or days) memory impairments, and short to medium changes in affect. To date the reported occurrence of seizure is small. However, the incidence of adverse effects could increase as stimulation is used

with more diverse populations. We encourage researchers to carefully monitor their experiments when using rTMS with subject populations who have an underlying brain injury (TBI, stroke, epilepsy) that could increase the risk of seizure or in subjects where there might already be diminished cognitive capacity or structural reorganization. Researchers should be aware that subjects do not always fully disclose what medications they take. Subjects can neglect to mention a history of childhood seizures if they believe they have recovered from whatever condition caused such seizures.

Researchers should take care when using TMS with subjects taking medications that alter depolarization thresholds, such as antidepressants or antiepileptics. Studies have shown that drugs working on the GABAergic system lengthen the refractory period immediately after the TMS pulse. This is believed to reflect intracortical connectivities. Drugs which effect sodium and calcium channels influence the baseline cortical excitability to a first pulse train. Although single-pulse TMS has been used with children, as of yet no repetitive TMS (rTMS) experiments have been reported.

Mike Gazzaniga (Dartmouth College) stated that cognitive neuroscientists should weigh the value of the information gained against the risk of harm when considering using rTMS on normal, healthy subjects – particularly in light of the possible long-term effects. Researchers actively using TMS in their laboratories reiterated that the risk for normal, healthy subjects was small. Near the end of the workshop, Susan Fitzpatrick (JSMF) asked the participants about their willingness to be subjects in a TMS experiment, based on what they had learned in the workshop. Less than half indicated they would volunteer.

SUMMARY

The results presented at the symposium suggest that rTMS has potential for studying cognitive processes but that there are a number of issues that should cause the cognitive neuroscience community to be cautious in its use. The paramount issue is the safety of the method. Safety parameters for rTMS need to be rigorously established as they have been previously for single pulse TMS. Among the specific suggestions were: 1) it is essential for scientists using rTMS to make cognitive and behavioral assessments of their subjects before and after rTMS studies. There could be some benefit is following a group of subjects long-term; 2) animal studies establishing the cellular alterations and possible damage resulting from rTMS must become a priority; and 3) all investigators who use rTMS, including students and postdoctoral fellows, should be trained on the existing (and hopefully forthcoming) safety guidelines and how to respond in the case of an emergency.

If cognitive neuroscientists hope to fully understand the neural substrates of cognition, then it is essential that serious efforts be made to understand what it is that brain imaging/brain sensing techniques measure and what they can and cannot tell us about the neural underpinnings of cognitive processes. Brain imaging techniques sense underlying neuronal activity where rTMS provides the investigator with the ability to alter neuronal function in spatially resolved regions. It is presently the only method allowing selective perturbation of brain function. It is also essential that the experimental cognitive tasks be carefully selected to provide information about brain processes at a level of analysis comparable to that being monitored neurobiologically. Such a knowledge base is even more critical when it comes to the interpretation of TMS experiments. TMS is not a non-invasive brain imaging tool. Cognitive neuroscience insights drawn from TMS experiments derive from perturbing normal brain function. It is possible that rTMS used in combination with fMRI, PET, and EEG, will provide new information on brain structure/function relationships, learning and plasticity, the interactions among different brain regions, and how different neurotransmitter systems influence cognitive function. But to live up to its potential, it is essential that the safety of the method be established and the alterations in brain function induced by rTMS be fully explored.

***Selected references*:**

1) The February 1999 *Neuropsychologia* (volume 37, no.2) is a special issue titled TMS in Neuropsychology , guest edited by Vincent Walsh and Matthew Rushworth. The issue contains 13 papers describing a variety of TMS applications to studies of brain structure/function.

2) For a review of TMS effects on cortical function see Transcranial magnetic stimulation: studying the brain-behaviour relationship by induction of 'virtual lesions' by Alvaro Pascual-Leone, David Batres-Faz, and Julian P. Keenan, *Phil. Trans. R. Soc. Lond.* B (1999) 354, 1-10.
3) The results of an international worshop on the risk and safety of repetitive-pulse TMS are summarized in a paper by Eric M. Wassermann in *Electroencephalography and clinical Neurology* (1998) 108, 1-16.
4) For data on the effects of TMS on neurotransmitter systems see: Chronic repetitive transcranial magnetic stimulation alters B-adrenergic and 5-HT_2 receptor characterisitics in rat brain. Dorit Ben-Shackar, Haifa Gazawi, Judith Riboyad-Levin, and Ehud Klein, *Brain Research* (1999) 816, 78-83.
5) For details on calculation methods for determining induced currents by time varying magnetic fields see Collins CM. Li S. Smith, M.B. SAR and B1 field distributions in a heterogeneous human head model within a birdcage coil. Specific energy absorption rate. *Magnetic Resonance in Medicine*. (1998) 40(6):847-56.
6) A good summary of TMS effects on learning and plasticity is found in Cohen LG, Ziemann U, Chen R, Classen J, Hallet M, Gerloff, C, and Butefisch C. Studies of neuroplasticity with transcranial magnetic stimulation. *Journal of Clinical Neurophysiology*. (1998) 15 (4):305-324.