Noninvasive Brain Stimulation in the Study of the Human Visual System

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Abstract: There are currently two techniques to manipulate brain function non-invasively: transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). These brain stimulation techniques work to cause long-term change within the brain. We have been combining noninvasive brain stimulation with functional magnetic resonance imaging (fMRI) to investigate the plasticity of brain networks. When fMRI is used as an outcome measure, it is possible to identify the specificity of tDCS-modulated plasticity in a visual rehabilitation protocol. Alternatively, fMRI can be used as a guide for stimulation. Brain stimulation with TMS affects neural networks, and fMRI guidance combined with an understanding of network effects of TMS may improve TMS therapy.

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Over the past 25 years, non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have become prominent as methods which can non-invasively introduce change within the brain for neuroscientific investigation and clinical treatment. Given the extensive knowledge about the anatomy and physiology of the human visual system, a fair number of studies have explored potential applications of TMS and tDCS to the visual system.[1,2]

EVOKING VISUAL EXPERIENCES WITH TRANSCRANIAL MAGNETIC STIMULATION

TMS, first introduced by Barker et al,[3] uses principles of electromagnetic induction to electrically stimulate neural tissue near the skull. When a transient change in electrical current is passed through a coil of wire, a transient magnetic field will be generated. The change in magnetic field induces a secondary electrical current in nearby conductors. In case of TMS, the secondary conductor is the cerebral cortex. Using this technique, it becomes possible to electrically stimulate neural pathways with only a coil of wire on the scalp.

When TMS is applied with a single pulse to motor or sensory cortex, it is possible to evoke a motor or sensory response. When the sensory cortex is visual cortex, the response is a phosphene.[4] Phosphenes are the sensation of light in the absence of visual stimulation. Phosphenes caused by TMS to occipital cortex are subjectively weak in appearance, and generally require TMS-naive participants to wear blindfolds to limit extraneous visual information in order to identify the location of the phosphene in the participant's visual field. Phosphenes generated from the visual cortex are retinotopically mapped in correspondence to the representation of cortex, and more complex phosphenes such as moving phosphenes can be elicited from stimulation of visual areas responsible for motion. Phosphenes can be elicited in blind participants if the neural tissue to be stimulated is intact and the cortical read-out of the vision–deprived visual cortex remains unchanged.[5]

Because neurons are connected to other neurons, stimulation of one population of cells will evoke responses in synaptically connected brain regions. Thus, the area of the brain stimulated by TMS will affect activity in specific brain networks. To best illustrate this effect, we recorded functional magnetic resonance imaging (fMRI) of the brain from a subject who received occipital stimulation to evoke phosphenes. Figure 1 shows the placement of the TMS coil in the scanner. In order to ensure the TMS pulse did not interfere with MRI acquisition, the TMS pulse was interleaved with MRI volume collection. Stimulation was applied at 110% of phosphene threshold (the stimulation intensity needed to elicit phosphenes in at least half of the trials) measured inside the bore of the scanner. Given the placement of the coil in this particular case, stimulation resulted in the perception of a phosphene in the upper right visual field (Fig. 2). Consistent with the retinotopic organization of primary visual cortex within the calcarine sulcus, corresponding activation was found in the lower left V1. However, there is additional activity outside of calcarine sulcus which is correlated with the TMS pulse. For example, the application of TMS to the occipital pole targeting striatal cortex resulted in activity in the lateral temporal-occipital region in both right and left hemispheres, as well as activity along the intraparietal sulcus, regions known to be visually responsive. Thus, although TMS is only applied locally, the effects of TMS spread through existing connections within the cortical visual system. This integration of TMS with fMRI therefore provides a unique tool to study human brain functional connectivity in vivo and assess how it might be altered by certain interventions, behaviors, or pathologies.

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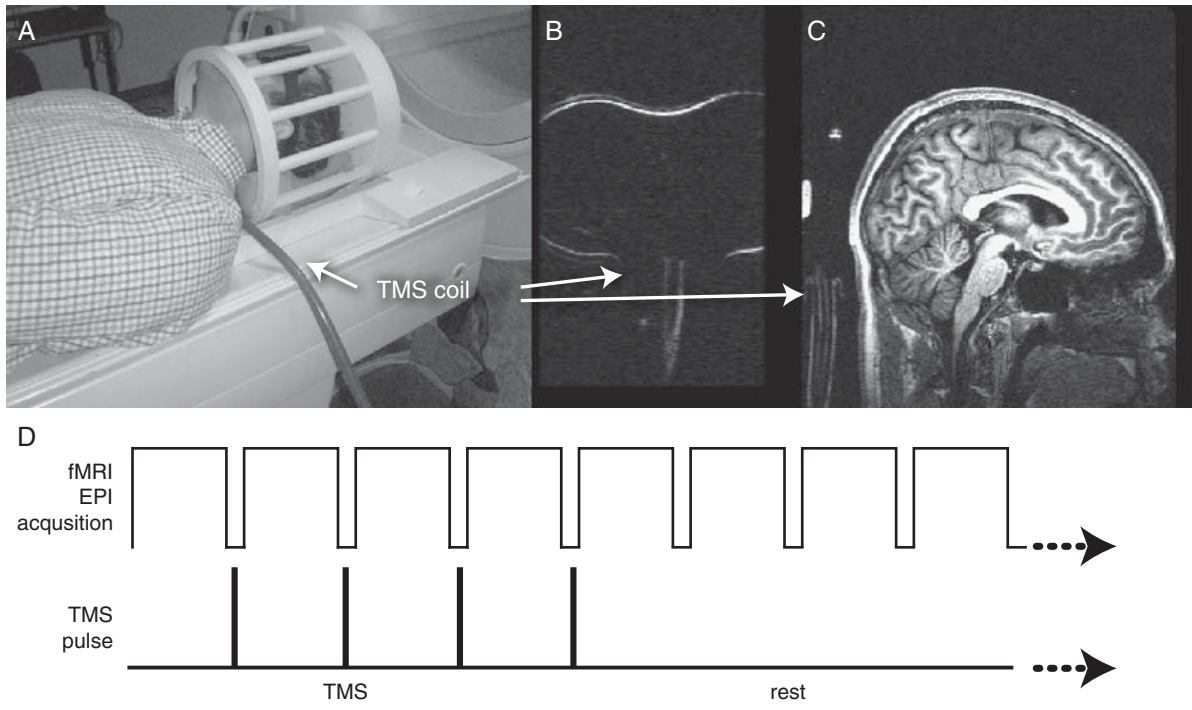

FIGURE 1. Online occipital transcranial magnetic stimulation with functional magnetic resonance imaging (TMS-fMRI) experimental setup. A, photograph of a subject in position for TMS to occipital pole. The subject lies in a supine position, and the TMS coil is placed under the head. B, coronal and C, sagittal views of the TMS coil and head position. An outline of the TMS coil is visible. D, experimental paradigm, TMS is interleaved between each fMRI volume acquisition, for a period of 20 seconds, followed by 20 seconds of rest.

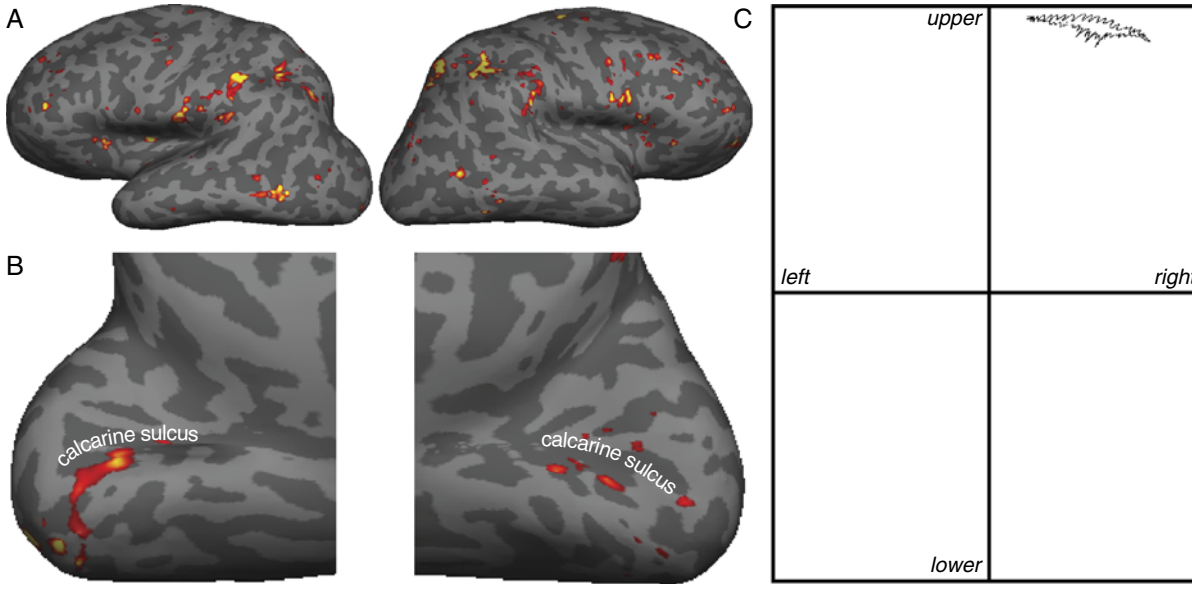

FIGURE 2. Results of one subject's online transcranial magnetic stimulation with functional magnetic resonance imaging (TMS-fMRI) experiment. A, Lateral views of an inflated surface representation of cortex with areas which have increased activity during TMS rendered in red-yellow. B, Medial views of the occipital lobe with fMRI activation. C, Subject's representation of the location of the perceived phosphene during TMS-fMRI. The subject's perception of the phosphene in the upper right visual field matches the activation observed in the ventral left calcarine sulcus. Additional activation in commonly activated visual areas is observed in frontal, parietal and lateral occipito-temporal cortex.

PROLONGED EFFECTS FROM NONINVASIVE BRAIN STIMULATION

The effects of single pulses of TMS are extremely brief, lasting a few milliseconds. Strongly influenced by studies of synaptic plasticity (long-term potentiation and long-term depression), stimulation protocols have been developed where the effects of stimulation can persist for a few minutes after stimulation ends.[6] More complicated pulse sequences, such as 'theta-burst' stimulation, can lead to changes in cortical excitability which can persist as long as an hour following stimulation.[7] These repetitive stimulation protocols can be used to induce lasting change in activity in the targeted brain region and modulate the state of activity across a specific brain network. For example, these protocols have been successfully applied for treatment of depression. Repetitive TMS targeting dorsolateral prefrontal cortex in daily treatments for 4–6 weeks could alter activity in the cortico-subcortical network that mediates mood. This intervention was safe and effective in patients with medication-resistant depression.[8]

TMS is not the only noninvasive stimulation paradigm which can induce prolonged effects. Recently, a revival of electrical stimulation techniques has renewed interest in transcranial direct current stimulation (tDCS). In its simplest form, two large saline soaked pads are placed on the head. To increase cortical excitability, the anodal pad is placed over the site of interest; to decrease cortical excitability, the cathodal pad is placed over the site of interest.[9] These changes in cortical excitability can last as long as 20–30 minutes when applied to visual cortex.[10] As with TMS, tDCS can be used repeatedly in daily sessions to induce lasting effects through modulation of brain network plasticity.

Prolonged effects of noninvasive brain stimulation have been investigated in other clinical domains beyond depression, such as focal epilepsy, Parkinson's disease, chronic pain and stroke recovery.[11] In stroke or other brain lesions, non-invasive brain stimulation can be used to promote recovery and is particularly powerful when accompanied by rehabilitation. Visual rehabilitation[12] and motor cortex[13] were observed. Currently, the methodology and devices exist for neuromodulation, but our understanding of how the visual system recovers function is still fairly rudimentary.[14,15]

In summary, noninvasive brain stimulation techniques can be used to probe existing visual abilities in the absence of retinal input and to alter neural circuits for prolonged periods of time. A better understanding of the neural networks involved in vision will allow for more precise treatment strategies to restore lost visual function or enhance existing vision.

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