CORRESPONDENCE

Enhancing Putative Mirror Neuron Activity with Magnetic Stimulation: A Single-Case Functional Neuroimaging Study

To the Editor:

Mirror neuron-driven embodied simulation, based on the neural exploitation hypothesis has been proposed as a physiological basis of social cognitive abilities in humans (1). Experimental evidence points to a relationship between social cognition and putative mirror neuron activity in neuropsychiatric disorders like schizophrenia (2) and autism (3). Experiments to explore strategies to modulate mirror neuron activity (MNA) are rare (4). We are unaware of any previous report that applied targeted brain stimulation to improve functional magnetic resonance imaging (fMRI) blood oxygen level-dependent (BOLD) activation during action observation paradigms, an indirect method of measuring MNA. Transcranial magnetic stimulation (TMS) is a safe, noninvasive method of administering targeted brain stimulation (5) to enhance focal brain activity. In this letter, we describe the first report of a single session of high-frequency repetitive TMS (HF-rTMS) delivered at the left inferior frontal gyrus (IFG) enhancing putative MNA as ascertained by functional magnetic resonance imaging (MRI).

Subject

A 38-year-old consenting, right-handed, male volunteer, with no psychiatric/neurological disorder and no contraindications for TMS (assessed using TMS Adult Safety Screen [6])/MRI procedures, was examined using fMRI for putative MNA.

TMS Procedures

High-frequency repetitive TMS was applied to the left IFG. To determine the stimulation area, we used Montreal Neurological Institute coordinates ($x = -59$ mm, $y = 11$ mm, $z = 25$ mm) from a previous fMRI study that investigated mirror neuron properties of left IFG (7). The Talairach coordinates for left IFG were translated into International 10-20 System scalp coordinates using Münster T2T-Converter (http://wwwneuro03.uni-muenster.de/ger/t2tconv/conv3d.html). Stimulation was applied using a 70-mm diameter figure of 8 coil (MagPro R100 with MagOption; MagVenture, Farum, Denmark) to the left IFG at 20 Hz (8), with 100% resting motor threshold. Forty-five trains, each comprising of 40 pulses per train (2 seconds per train) with intertrain interval of 28 seconds, were administered (total of 1800 pulses). Sham stimulation was delivered at the same site as active stimulation with the sham coil, which provided only an equivalent auditory stimulus. The subject was blind to true versus sham TMS. For both true and sham stimulations, the coil was positioned with the handle at 45° to the sagittal plane. The current flow in the TMS coil induced a posterior-to-anterior current flow in the underlying cortex. Figure 1.

fMRI Paradigm

The fMRI paradigm was designed using E-Prime (Psychology Software Tools, Pittsburgh, Pennsylvania) and projected within the MRI scanner using E-Sys (Invivo, Gainesville, Florida). A liquid crystal display monitor was placed at 6 feet from the head of the subject to project the stimuli. The subject was instructed to passively look at the reflecting mirror placed in front of the eyes mounted within the MRI head coil that enabled him to see the monitor. The fMRI paradigm consisted of three different types of conditions: 1) dynamic pincer grasp action: a video clip of 8-second duration showing a right hand grasping the mug on the breakfast table in a pincer grasp and lifting it, representing a goal-directed action; 2) dynamic control: another video clip of 8-second duration showing a fisted right hand, withdrawing from the breakfast table, representing a nongoal-directed action (both the dynamic blocks were of 32-second duration, each with the video clip being shown repeatedly for four times in a loop); and 3) static control: a still image of a hand placed flat on the same breakfast table background as that shown in the other blocks (16-second duration). The order of the blocks was static control-dynamic control-static control-dynamic pincer grasp action with five repetitions of this sequence resulting in a total 8-minute duration constituting a single run. The subject was instructed to passively observe the projected stimuli during two runs of the paradigm at three different time-points: 1) baseline (before any TMS procedures); 2) true TMS (5 minutes following true HF-rTMS); and 3) sham TMS (5 minutes following sham HF-rTMS), in that order.

Image Acquisition and Analysis

Functional MRI was acquired using a 32-channel coil in a 3-Tesla MRI scanner (Magnetom Skyra, Siemens, Erhlangen, Germany) (repetition time = 2000 msec; echo time = 30 msec; flip angle = 78°; slice thickness = 3 mm [1-mm gap]; 37 slices; field of view = 192 × 192; 3-mm isotropic voxel). Using Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurobiology, University College of London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm/), the images were realigned, spatially normalized, and smoothened (8-mm kernel) followed by first-level design specification and estimation. Evidence for significantly increased BOLD activation in the a priori region of interest (a 10-mm radius sphere, the coordinate of HF-rTMS application as its center) during the dynamic pincer grasp action observation relative to the dynamic control action observation, following true TMS in comparison with the other two conditions (namely, baseline and sham TMS), was evaluated using the contrast [post-TMS > (baseline + sham TMS)]. This revealed significantly greater BOLD activation (Figure 1) during true TMS stimulation (Brodmann area 45, Montreal Neurological Institute coordinates [$x = -62$, $y = 16$, $z = 24$], $t = 2.05$, $p = .02$ [uncorrected since there is only one a priori region of interest]); no enhanced activation was observed during the sham TMS condition.

Discussion

To the best of our knowledge, this is the first demonstration of enhancement of putative MNA using targeted brain stimulation in a human subject. This single-case experiment, however, needs further systematic evaluation and replication through more rigorous studies with larger samples. We found that putative MNA in the left IFG was significantly greater following true TMS when compared with that at baseline and after sham TMS. Performing sham TMS last negated the possibility of practice effect benefiting true TMS. The left IFG was selected for stimulation, as it is presumed to be the homologue of F5 in monkeys where mirror neurons are located. Moreover, pars

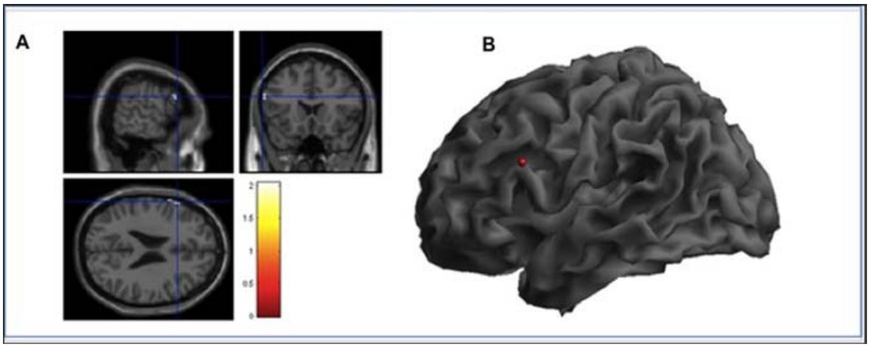

Figure 1. **(A)** Significantly greater activation during the dynamic pincer grip condition in the left inferior frontal gyrus, corresponding to Brodmann Area 45, after true transcranial magnetic stimulation is shown. **(B)** Surface rendered view of the brain with the red spot representing the left inferior frontal gyrus region where putative mirror neuron activity enhancement was observed.

triangularis (Brodmann area 45), the region in which activation was observed, has been shown to demonstrate mirror neuron activation while viewing grasping action in human subjects (9). Excitation of the underlying mirror neuron regions could be due to greater transsynaptic glucose metabolism (10) or by augmentation of gamma oscillatory activity (8). Both these mechanisms have been demonstrated to be operative with 20-Hz HF-rTMS. Modulation of MNA can potentially lead to vital insights regarding the neurobiology of social cognitive deficits with possible translational therapeutic applications in psychiatric disorders in which mirror neuron aberrations have been implicated.

Urvakhsh Meherwan Mehta[a*]
Sri Mahavir Agarwal[a,b]
Sunil V. Kalmady[a,b]
Venkataram Shivakumar[a,b]
C. Naveen Kumar[a]
Ganesan Venkatasubramanian[a,b]
Jagadisha Thirthalli[a]
Bangalore N. Gangadhar[a]
Alvaro Pascual-Leone[c]
Matcheri S. Keshavan[d]

[a]Department of Psychiatry and [b]Translational Psychiatry Laboratory, Cognitive Neurobiology Division, Neurobiology Research Centre, National Institute of Mental Health & Neurosciences, Bangalore, India; and [c]Berenson-Allen Center for Noninvasive Brain Stimulation, Department of Neurology, and [d]Department of Psychiatry, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, Massachusetts.

*Corresponding author E-mail: urvakhsh@gmail.com.

This research work is supported by the Wellcome Trust/Department of Biotechnology India Alliance Senior Fellowship Research Grant to GV. SVK is supported by Wellcome Trust/Department of Biotechnology India Alliance. VS is supported by the Indian Council of Medical Research.

The authors report no biomedical financial interest or potential conflicts of interest.

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http://dx.doi.org/10.1016/j.biopsych.2013.02.009