Investigation of Anatomical and Effective Connectivity using White Matter Tractography and Transcranial Magnetic Stimulation

M. Lazar[1], M. Massimini[2], F. Ferrarelli[2], B. A. Riedner[2], J. H. Lee[1], A. L. Alexander[1,3], G. Tononi[2]

[1]Waisman Center, University of Wisconsin, Madison, WI, United States, [2]Psychiatry, University of Wisconsin, Madison, WI, United States, [3]Medical Physics, University of Wisconsin, Madison, WI, United States

Introduction: Higher brain functions are realized through communication between different neural centers situated in brain gray matter. Neural connectivity is related to structural connectivity networks provided by white matter pathways. White Matter Tractography (WMT) uses directional information provided by DTI to estimate white matter tracts course and anatomical connectivity between different brain regions (1). Transcranial Magnetic Stimulation (TMS) is a non-invasive method of stimulating the brain (2). Effective interactions of the stimulated points with other cortical regions may be obtained by recording the evoked spread of brain activation using high-resolution electroencephalography (HR-EEG). The goal of this study was to compare the anatomical connectivity patterns obtained using WMT with the effective connectivity patterns obtained using TMS/EEG. Whereas both DTI/WMT and TMS/EEG have been previously applied in separate studies with results consistent with generic known anatomy, no studies comparing anatomical and effective connectivity on individual basis have been yet conducted.

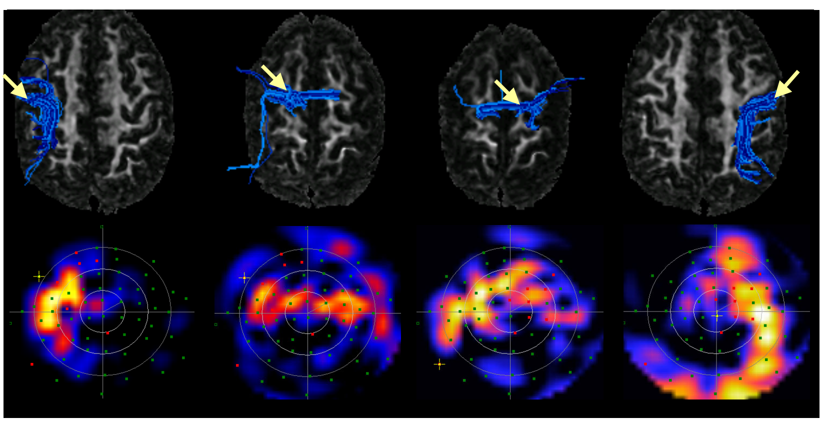
Methods: Diffusion Tensor Imaging: DTI images were obtained on a 3T MRI scanner using a cardiac-gated single-shot spin-echo EPI pulse sequence with diffusion-weighting gradients applied in 12 uniform distributed encoding directions (3). The acquisition for each encoding direction was repeated three times and combined using magnitude averaging. Thirty-nine axial slices (3mm thick) were acquired to cover the cerebrum. The original voxel size was 0.94x0.94x3 mm^3, which was interpolated to isotropic dimensions. The total imaging time was 7-8 minutes. Image misregistration from motion and eddy current distortion was corrected using a 2D affine registration algorithm in AIR (4). Field map correction was subsequently applied to correct for EPI distortions resulting from B_0 inhomogeneities. White Matter Tractography: Fiber trajectories were estimated using the streamline algorithm (1) with a second-order Runge-Kutta integration method. Medial and lateral regions situated in the premotor and somatosensory cortices were chosen as seed regions for white matter tractograms. These seed regions corresponded to premotor and somatosensory cortical terminations of the superior longitudinal fasciculus and the corpus callosum tracts.

Transcranial Magnetic Stimulation: TMS experiments were performed using a figure-of-eight coil design (Magstim Company Limited, Spring Gardens, Whitland, Wales, UK). The cortical regions that were used as WMT seed regions were chosen as TMS sites. A frameless stereotactic method, which provides an estimation of the TMS hot spot on the cortical surface, was used for coil positioning. EEG data was recorded using a TMS/EEG acquisition system (Nexstim, Helsinki, Finland), with 60 EEG channels (1 kHz digitization). Post-acquisition, the distribution of neural activity as a function of time was generated using a minimum norm estimate (MNE), a multidipole model that uses a generic head model that consists of four concentric layers of different conductivities (scalp, skull, cerebrospinal fluid, and brain).

Results: Combined DTI/WMT and TMS/EEG studies were conducted in three healthy subjects. In two subjects, TMS stimulation (200 pulses) was applied to left and right medial and lateral premotor areas. In the third subject, the TMS stimulation was applied to left and right medial and lateral somatosensory regions. Figure 1 shows the positions of TMS stimulation points in subject 1, which were also used to define the seeding regions for WMT. WMT tractograms are overlaid onto subject axial FA maps. Cortical activation, for each stimulation point, at 50 ms after the TMS pulse, is shown in Figure 1, bottom row. The potential distribution and the tractograms both demonstrate greatest patterns of connectivity in the anterior/posterior direction for the lateral stimulus points, through pathways of the superior longitudinal fasciculus, whereas the medial stimulus points show greater interhemispheric connectivity in the right/left direction through the corpus callosum. Similar results were obtained for subject 2. White matter tractograms, stimulations points, and corresponding activation maps for subject 3, at 20 ms after the TMS pulse, are shown in Figure 2, for the right hemisphere. The lateral somatosensory cortex shows primarily intrahemispheric anatomical and effective connectivity patterns, whereas medial somatosensory cortex appears to be primarily connected interhemispherically, to homologous contralateral regions.

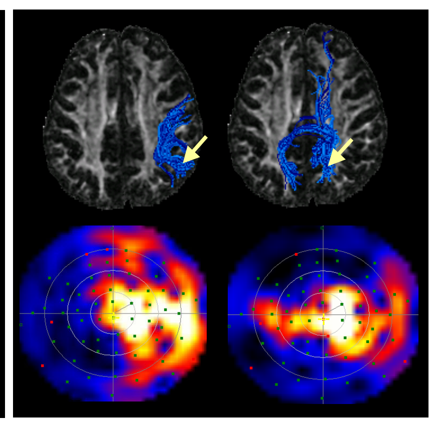
Discussion: This study demonstrates for the first time the combined application of DTI/WMT and TMS/EEG. Similar patterns of anatomical and effective connectivity were found in each subject. The sets of medial-lateral regions investigated in this study were relatively closely situated to each other; however they exhibited markedly different anatomical connectivity patterns. The similar results obtained using the two different modalities are promising for synergetic multimodal studies of brain connectivity. Future studies will investigate correlations between measures of effective connectivity, such as arrival times for the cortical activation spread, with measures of anatomical connectivity derived from WMT/DTI, such as connection volumes and tract anisotropy.

References: **1.** Mori S and Van Zijl PC. *NMR Biomed* 2002;15:468-480; **2.** Ilmoniemi RJ et al. *Crit Rev Biomed Eng* 1999;27:241-284; **3.** Hasan KM et al. *J Magn Reson Imaging* 2001;13:769-780; **4.** Woods et al. *J Comp Ass Tom* 1998;22:141:154;



(a) (b) (c) (d)

Figure 1. WM tractograms and cortical activation maps for (a) left lateral premotor cortex, (b) left medial premotor cortex, (c) right medial premotor cortex, and (d) right lateral premotor cortex (subject 1). The positions of the seed/stimulation regions in each case are indicated by arrows. The cortical activation maps shows strong activation in light-yellow regions.



(a) (b)

Figure 2. WM tractograms and cortical activation maps for (a) right lateral sensory cortex, and (b) right medial somatosensory cortex (subject 3). Stimulation/ seed regions are indicated by arrows.

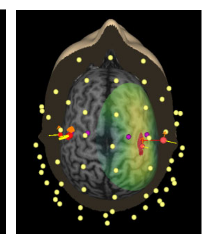


Figure 3. Placement of the EEG electrodes relative to the brain surface. The TMS hot spot (for right lateral premotor cortex, subject 1) is shown in dark red.