Co-registration of Magnetic Resonance Spectroscopy and Transcranial Magnetic Stimulation

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Objective: To validate a pipeline to register an MRS voxel location in the motor cortex for transcranial magnetic stimulation (TMS).

Background: MRS can estimate the *in vivo* concentrations of glutamate and GABA *in vivo*, the main excitatory and inhibitory neurotransmitters in the human brain. Different TMS protocols targeting the primary motor cortex (M1) can provide measures of cortical excitability and inhibitory function. It is likely that the combination of MRS and TMS will become increasingly common in clinical studies, to probe the altered excitation/inhibition balance found in many neurological, psychiatric and neurodevelopmental disorders, and to investigate the neurochemical mechanisms underlying the various TMS protocols. Co-localization between the MRS voxel and the application of TMS is required for such studies, and a pipeline is needed for integrating MRS voxel location into the sophisticated stereotaxic neuronavigation systems (such as Brainsight (Rogue Research Inc, CAN)) used to accurately target the region to be stimulated. Here we present a protocol to allow visualization of MRS voxel location during neuronavigated TMS and validate the process by assessing the overlap between an M1 MRS voxel and the vector of TMS stimulation that induces a motor evoked potential (MEP) from the first dorsal interosseous (FDI) muscle at rest as recorded by EMG.

Methods: 16 participants were recruited and scanned at 7T (Philips Achieva, The Netherlands) prior to TMS. MR scanning included a 1mm^3 isotropic resolution T_1-weighted anatomical acquisition (MPRAGE) of the whole head, including the tip of the nose (needed for TMS target registration). MRS was performed in a (25 mm)^3 voxel within the right M1, including the motor hand knob . The voxel position was then co-registered to the T_1-weighted image and converted to a binary mask using custom software written in IDL.

TMS-induced MEPs were recorded from the FDI muscle while participants were at rest. The average stimulation intensity to reach the motor threshold was 50.5±9.7%. TMS pulses were delivered over the right M1 with a commercially available 80-mm figure-of-eight coil and a Magstim Stimulator. The current waveform was biphasic and the orientation of the stimulation coil was 45˚ from the midline with the handle pointing backwards. Resting motor threshold and optimal scalp site to induce MEPs were defined as the minimum TMS intensity required to induce MEPs of > 50mV peak-to-peak amplitude in at least 5 of 10 trials in the contralateral FDI muscle. Relaxation of the FDI muscle was documented by EMG recording for at least 40 msec before each TMS pulse. MEPs were recorded using pairs of Ag/AgCl surface electrodes placed over the FDI. Neuronavigation was performed using Brainsight and Polaris Spectra (Northern Digital, USA) optical tracking. A virtual head model was constructed for all participants prior to TMS. The combination of the virtual head model and additional markers over the TMS coil were used to control its localization relative to the head. These steps are summarized in Figure 1. Correspondence between the MRS voxel and the TMS target localization was examined within Brainsight and deemed successful if the coil-perpendicular vector intersected the MRS voxel.

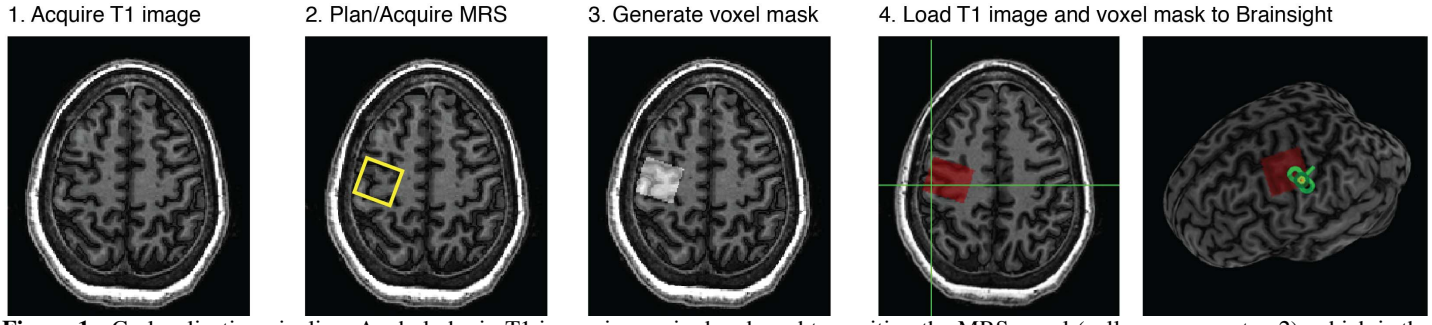

Figure 1. Co-localization pipeline. A whole-brain T1 image is acquired and used to position the MRS voxel (yellow square, step 2), which is then converted into a mask in step 3. This mask is used for TMS localization in step 4. The green crosshair is the intersection of the TMS perpendicular vector and the slice of the image, shown with the voxel mask in red. The green "8" displays the position and orientation of the TMS coil.

Results: An independent review of images indicated that all MRS voxels were included the motor hand knob. The TMS coil-perpendicular vector passed through the reconstructed MRS voxel in 14 of 16 subjects. In one case of discrepancy, the TMS vector was parallel to one face of the MRS voxel, less than 1 mm away. In the second, technical difficulties and study-timing limitations prevented accurate registration during the TMS session. In this case, TMS was performed without reference to the Brainsight system.

Discussion: Studies that combine TMS and MRS to investigate cortical excitability/inhibition will benefit from a co-localization pipeline. Within the developed pipeline, there are two stages at which a mismatch between the MRS voxel location and TMS coil location to generate MEPs can occur. The first, misplacement of the MRS voxel, is minimized by technologist training and identification of reliable anatomical landmarks. The second, imperfect co-registration between the virtual head model in Brainsight and laboratory space, can arise due to a number of factors, including inaccurate identification of landmarks on the scalp, or imperfect anchoring of the stereotaxic markers to the head.

Conclusion: A registration and co-localization pipeline to integrate MRS and image-guided TMS has been developed and validated for a motor protocol with the MRS voxel at the hand-knob in M1 and TMS directed at M1 (as demonstrated by MEPs).

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