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Co-registration of Magnetic Resonance Spectroscopy and Transcranial Magnetic Stimulation

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Abstract

Transcranial magnetic stimulation (TMS) is a widely used tool for noninvasive modulation of brain activity, that is thought to interact primarily with excitatory and inhibitory neurotransmitter systems. Neurotransmitters such as glutamate and GABA can be measured by magnetic resonance spectroscopy (MRS). An important prerequisite for studying the relationship between MRS neurotransmitter levels and responses to TMS is that both modalities should examine the same regions of brain tissue. However, co-registration of TMS and MRS has been little studied to date. This study reports on a procedure for the co-registration and co-visualization of MRS and TMS, successfully localizing the hand motor cortex, as subsequently determined by its functional identification using TMS. Sixteen healthy subjects took part in the study; in 14 of 16 subjects, the TMS determined location of motor activity intersected the (2.5 cm)³ voxel selected for MRS, centered on the so called 'hand knob' of the precentral gyrus. It is concluded that MRS voxels

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placed according to established anatomical landmarks in most cases agree well with functional determination of the motor cortex by TMS. Reasons for discrepancies are discussed.

Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation technique that uses the principles of electromagnetic induction to induce an electric current within the surface of the human cortex. This current may be of sufficient intensity to depolarize neurons in a certain area (Wagner et al. 2009). Single-pulse and paired-pulse TMS paradigms can be used in the evaluation of cortical excitability with measurements of short interval cortical inhibition (SICI), intracortical facilitation (ICF), and long interval cortical inhibition (LICI) (Kujirai et al. 1993). These measurements of the motor cortex excitability are widely applied in cognitive and clinical neuroscience, for example, to assess cortical function or neuronal damage in neurological conditions (Bares et al. 2003; Pascual-Leone 2006) and to measure the effect of pharmacological compounds (Feil and Zangen 2010). If administered repetitively, TMS may elicit significant cortical excitability changes that outlast the period of stimulation. These long-lasting changes are associated with neuronal plasticity and may promote cognitive and behavioral changes (Wassermann and Lisanby 2001). TMS applied to the primary motor cortex with electromyographic (EMG) recording of motor-evoked potentials (MEPs) remains the standard in motor electrophysiology (Hallett 2007).

¹H magnetic resonance spectroscopy (MRS) is a noninvasive method for *in vivo* detection of endogenous tissue metabolites. When performed in the human brain at 7 Tesla, it allows the estimation of the concentration of up to 17 different neurochemicals (Tkac et al. 2009), including N-Acetyl-Aspartate (NAA), choline (Cho), creatine (Cr), glutamate (Glu), glutamine (Gln), γ -aminobutyric acid (GABA) and *myo*-inositol (mI). At the more commonly available field strength of 3T, MRS with spectral-editing is being increasingly used to measure GABA (the principal inhibitory neurotransmitter) for studies of cognitive neuroscience and assessment of motor-cortical plasticity (Puts and Edden 2012; Stagg 2013).

The combination of MRS and TMS is also becoming increasingly studied (McKeefry et al. 2009; Ruff et al. 2009; Thut and Pascual-Leone 2009). MRS has been used in combination with TMS to show that TMS measures of cortical inhibition (Tremblay et al. 2013) and cortical excitability (Stagg et al. 2011) may depend on concentration and transmission changes in cortical Glu. The effects of TMS are dependent on different parameters, including the location and angular placement of the coil, the intensity, the frequency and timing of the pulses, state dependence and excitability measure (Pell et al. 2011). Therefore, standardization of stimulation protocols is particularly important for proper results interpretation. Brainsight™ 2 (Rogue Research Inc., CAN), a state-of-art frameless stereotaxic neuronavigation system, allows visual guidance of the coil placement, relying on previously acquired MR anatomical information of each individual. Such neuronavigation systems have been extensively used in the mapping of cortical regions and limit intrasubject variability (Gugino et al. 2001; Bashir et al. 2013).

As an increasing number of studies use TMS to characterize the relationship between cortical excitability and GABA levels within the brain, validation of MRS and TMS co-registration is needed. The purpose of this study was therefore to demonstrate a workflow for combined TMS-MRS studies allowing the co-registration and co-visualization of MRS and TMS and to validate the concordance of MRS voxel localization and TMS-induced MEPs, in an effort to add supplementary precision to TMS protocols registered with MRS data.

Methods

Participants

Sixteen participants (mean age = 56 ± 10 years; 6 males; 14 right-handed) were included after providing written informed consent under local IRB approval.

MRI and MRS acquisition

All MR data were collected prior to TMS on a 7T scanner ('Achieva', Philips Healthcare, Best, The Netherlands), using a 32-channel head coil for receive and a head-only transmit coil (Nova Medical, Wilmington, MA). T1-weighted images were acquired using the MPRAGE sequence with (1 mm)³ isotropic resolution (TE/TR 3.7/8 ms). Given the motor function focus of this study, MRS data were acquired from a 2.5×2.5×2.5 cm³ voxel positioned by experienced MR technologists so as to include the motor hand knob (Yousry 1997), within the primary motor cortex on the precentral gyrus, and placed to minimize inclusion of postcentral tissue (see Figure 1). This voxel positioning is approximately 7 mm more anterior than the sensorimotor voxel as used in other recent studies (Puts et al. 2011; Evans et al. 2013). Figure 2 illustrates sample MR spectra obtained from the motor voxel.

Resting motor threshold with TMS

TMS was delivered using a Magstim BiStim² (Magstim, USA) monophasic system with a 70 mm figure-of-eight-shaped air-cooled coil. The coil was positioned flat on the head of each participant, with the center of the coil at the localization of the primary motor cortex (M1), at a 45 degrees angle from the midline. The induced current direction was posterior-anterior, perpendicular to the central sulcus. Two Ag/AgCl recording surface electrodes were positioned on the first dorsal interosseous (FDI) muscle and one ground electrode was positioned on the wrist. The resting motor threshold was measured in each participant, with its standard definition of reaching a 50µV peak-to-peak amplitude MEP in at least 5 times out of 10 with the lowest stimulator intensity. The interstimulus interval between TMS pulses was 10 sec minimum to minimize possible carry-over effects. TMS-induced MEPs and relaxation of the FDI was documented by EMG recording before each TMS pulse. The EMG signal was recorded using a AMT-8 system (Bortec Biomedical Ltd., CAN), filtered with a band pass of 10-500 Hz, and digitized at a sampling rate of 2 kHz. The average motor threshold intensity was 51.7 ± 2.5%.

Co-registration of MRS and T1 images

During MRI scanning, the T1-weighted anatomical image was used to locate the hand knob in the axial and sagittal planes (the motor cortex typically shows as a rear-facing hook in the

sagittal image, see Figure 1). Using header information from the MRI and MRS data, an image was reconstructed in the coordinate-space of the T1-weighted image representing the voxel location as a binary mask. This task was implemented (for images in Philips PAR/REC format and MRS data in SDAT/SPAR format) within the IDL tool SVMask (Michael Schär, Philips Healthcare, Netherlands).

Visualization of MRS voxel in neuronavigation system

The neuronavigation system Brainsight™ 2 (Rogue Research Inc., CAN) combined with the Polaris Spectra (Northern Digital, USA) optical tracking system were used with passive markers positioned on the participant's head (fixed to a pair of glasses) to model the virtual head of each participant, prior to stimulation procedures. Markers were disposed over the TMS coil to register its localization to the MRS voxel and brain target area. Co-registration requires the identification of anatomical landmarks on the surface of the head and in the MR image, typically the tip of the nose, the bridge of the nose and the inter-tragal notch of each ear, with the marker cursor. This allows the position of the head, relative to the Brainsight™ marker glasses, to be determined. By continuous tracking of the position of the markers and the TMS coil, the coil position can then be displayed within the three-dimensional space of the MR images. In this study, the MR image was presented with the MRS voxel mask as an additional overlay, as seen in Figure 3.

Data analysis

The main purpose of this study was to determine whether the coil position that elicited MEPs corresponded with the anatomically identified hand area and the position of the MRS measurement voxel. All cases were reviewed within Brainsight™ after the TMS session and successful co-registration of MRI and TMS. Correspondence was judged to have been achieved if the coil-perpendicular vector passed through the MRS voxel including the hand knob. A failure to intersect could be caused either by incorrect identification of the hand area during MRS planning (whether due to erroneous interpretation of standard anatomy, abnormal anatomy, or abnormal location of hand area within the anatomy), leading to voxel placement away from hand area and TMS vector trajectory, or imperfect co-registration of laboratory space to the MRI, due to user error or marker movement.

Results

The hand knob, representative of the hand motor area within M1 (Yousry 1997), was located in all subjects using the T1-weighted anatomical images. Of 16 subjects in the study, the central sulcus (both sides) showed the classic single-lobed hand-knob form in 23 instances, whilst 9 showed a two-lobed, or more complicated, form. Despite inter-individual anatomical differences, review of images suggested that the MRS voxel was successfully placed so as to include hand area in all cases.

During TMS administration, the TMS coil-perpendicular vector passed through the MRS voxel reconstruction in 14/16 subjects (87.5%). There were discrepancies in two of sixteen subjects. In one of these, the TMS direction vector ran parallel to one face of the MRS voxel at a distance of less than 1mm (counted as a miss under the criteria established). In the

second, user difficulties prevented accurate registration of the laboratory (TMS) space to the MR images within the time constraints of the study. TMS was continued based upon MEPs and without reference to Brainsight™. This is regarded as a technical/procedural failure, rather than evidence of discordance between the TMS vector and MRS voxel location.

Discussion

Combination of brain stimulation and neuroimaging is becoming a gold standard in assessing causality of structural and functional interactions (Bestmann and Feredoes 2013). MRS is particularly useful in this regard, as it allows for the noninvasive probing of GABA and Glu levels, the primary neurotransmitters for inhibitory and excitatory processes within the brain. Moreover, TMS has been shown to modulate the glutamatergic and GABAergic systems (Fitzgerald et al. 2009; Stagg et al. 2011; Tremblay et al. 2013), further advocating for the combination of TMS with MRS.

The current study has demonstrated that co-registration of TMS with MRS is feasible, and that prospective 7T MRS voxel location prescription can reliably localize hand motor cortex as subsequently validated by TMS.

Neuronavigation with the Brainsight™ system allows precise registration of anatomical landmarks using previously acquired T₁ MRI information. Co-registration relies upon the identification of anatomical landmarks (both physically and in the brain images), allowing the position of the TMS coil relative to the head MRI to be tracked (see Figure 4). A full biophysical model of TMS, including the focality, shape and depth of the stimulating magnetic field is still not fully resolved (Wagner et al. 2009). While it is likely that the region of brain tissue being excited to elicit MEPs lies within the MRS voxel in the majority of the subjects studied, in the absence of a full model for field attenuation and distortion by different tissues, it cannot be claimed that this study fully ‘validates’ the anatomical position of hand motor area. The concordance measure chosen (i.e. does the coil-perpendicular TMS vector pass through the MRS voxel?) is recognized to be simplistic since the magnetic field produced by the TMS coil extends substantially around the coil vector, even given the more focal field produced by a figure-of-eight coil compared to a circular coil. Conversely, the field produced by such a coil penetrates less deeply than does a single loop coil (Deng et al. 2013) and the coil vector extends beyond the effective range of the coil. Furthermore, validation was performed using a 2.5×2.5×2.5 cm³ voxel, and while it is encouraging that in the majority of our participants the TMS and MRS locations overlap, the intersection of the TMS vector with this voxel does not guarantee the accuracy of the MRI identification of the motor cortex, and registration procedures.

However, this demonstration of a workflow for visualizing MRS voxel locations within the TMS navigation environment and of the concordance between motor-directed measurement locations for the two disparate techniques provides an important foundation for future studies combining MRS and TMS. A failure to reach concordance could have resulted from either mis-identification of hand area for MRS voxel placement, or from poor co-registration of the MRI to the head using brainsight, or from instability during the TMS session e.g.

movement of the glasses-mounted markers, which apparently only occurred in one subject only in the current study.

In this study, we proceeded with acquiring MRS information prior to TMS administration. It can be argued that the reverse process may also be used in similar protocols. This would allow using neuronavigated, TMS-obtained coordinates of the hand motor area to define the voxel localization for MRS acquisition. A technical limitation to the latter approach would be the need for an anatomical T1-weighted image to perform neuronavigated TMS, thus necessitating 2 MR scans in total for a single subject. Moreover, this method could only be used when assessing TMS of the motor or visual areas, with MEPs and visual phosphenes as TMS-elicited responses, respectively.

In conclusion, a reliable workflow has been demonstrated for co-registering TMS and MRS data. This methodology will be useful in the future for investigating the functional effects of TMS, and in clinical studies of pathologically altered cortical excitability and inhibition.

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Highlights

1. We demonstrate a workflow of co-registration and co-visualization of TMS and MRS
2. TMS delivery over the MRS voxel of interest elicited a physiological response
3. MRS voxel location can reliably localize the motor cortex subsequently validated by TMS
4. Co-registration of TMS and MRS is feasible and will be useful in future neurophysiological studies

Figure 1.

Hand knob anatomy and MRS voxel location. A) T1-weighted axial images for the slice containing the hand knob in each of the sixteen subjects. Eight subjects showed the classic bilateral single-lobe hand knob; seven showed a more complicated two-lobed (or more) variant; one subject showed this form bilaterally. B) MRS voxel location (light gray) superimposed on the MRI. In the axial slice the voxel was positioned so as to include all of the hand knob and minimal postcentral tissue. The hand knob appears in the sagittal slice as a rear-facing hook.

Figure 2.

Sample MR spectra from the motor voxel illustrated in Figure 1. Voxel was placed using the hand knob visualized on the T1-weighted image and is 15.6 mL in volume.

Figure 3. Screen shots of Brainsight™ TMS navigation, including MRS voxel overlay. Panels A-C show sagittal, coronal and axial slices, respectively, of the MRI with MRS voxel overlaid in red. Panels D and E show two perpendicular planes that include the TMS-coil-perpendicular vector. F) “Curvilinear brain” MRI reconstruction produced in Brainsight, showing the MRS voxel and coil position.

Figure 4.

Photograph of the actual TMS setup. A) The TMS coil and glasses with markers allowing registration to the optical tracking system. B) The Brainsight™ interface displays the position of the TMS coil to the pre-established cerebral target and MRS voxel. C) Electrodes disposed on the subject's hand for recording of MEPs.