* Manuscript

Positional paper
(Cortex – Special Issue: Contribution of TMS to Structure-Function Mapping in the Human Brain)

Neuronavigation for transcranial magnetic stimulation (TMS): where we are and where we are going.

R. Sparing,[*,1,2] M.D. Hesse,[1] and G.R. Fink[1,2]

[1] Institute of Neuroscience and Medicine (INM-3), Cognitive Neurology, Research Centre Juelich, Germany
[2] Department of Neurology, University Hospital Cologne, Cologne, Germany

Short title: Navigation for TMS.

Key words: image-guided TMS; frameless stereotaxy; TMS aiming accuracy; rTMS; precision; stereotactic space; noninvasive brain stimulation.

* Correspondence to:

Dr. Roland Sparing, M.D.

Department of Neurology
University of Cologne
Kerpener Str. 62
50924 Cologne Germany
phone: ++49 – 221 – 4455
fax: ++49 – 221 – 7005
mail: roland.sparing@uk-koeln.de

Focal TMS is an excellent neurophysiological tool for studying basic motor as well as higher cognitive brain functions. In brain mapping studies using TMS, the precise and accurate positioning of the TMS coil over the targeted cortical site represents one of the most challenging aspects of the experimental procedure. Exact coil positioning is crucial for the correct interpretation of stimulation effects. TMS studies of higher cognitive functions may, however, display high inter-subject and between-group variability, since sulcal anatomy, cytoarchitecture and function do not correlate well in many brain areas (Brett et al., 2002). In this case, a clear strategy how to localize the target area as well as how to position precisely the TMS coil is indispensable. In the following, we delineate the key problems of neuronavigation for TMS and how they can be addressed by modern neuronavigational strategies:

Reference frame – group-based vs. individualised

Successful neuronavigation for TMS requires careful consideration of interindividual anatomical variability, in particular in case of target areas with large intersubject variability such as the prefrontal cortex or along the interparietal sulcus. For instance, the 10-20 EEG electrode system is based on the rough assumption that there is a consistent correlation between scalp locations and underlying brain structures across subjects. However, skull deformities as well as interindividual variability of the cerebral sulci may lead to variations of up to 20 mm in the different axes, with some electrode positions being associated with larger variability than others (Herwig et al., 2003; Okamoto et al., 2004). Another commonly used positioning strategy draws upon a reference point at which TMS directly elicits an objective response, e.g., muscle twitches (M1). Other brain areas are subsequently located in spatial relation to this reference point. Accuracy is likely to fall off with increasing distance: Whereas areas adjacent to M1, e.g., S1, can be determined with reasonable accuracy, the identification of more distantly located sites, e.g., in the frontal cortex, is less reliable (Herwig et al., 2001).

To better account for interindividual anatomical differences, image-guided frameless stereotaxic neuronavigation systems (SNS) have been developed for the use with TMS (e.g., Schoenfeldt-Lecuona et al., 2005; Wagner et al., 2007; Sparing et al., 2008). SNS use the subject's individual MRI for navigation via a subject-image coregistration procedure based on facial/cranial landmarks. Although the system's precision relies upon technical limitations, the quality of the MRI investigation and exact coregistration, the spatial deviations have been shown to lie within the millimeter range (Neggers et al., 2004; Schonfeldt-Lecuona et al., 2005).

Target definition I – anatomical vs. functional

Instead of using anatomical information (i.e., 10-20 EEG system or individual MRI) the TMS coil can also be positioned using a function-guided approach: If the TMS effect on the performance of a certain behavioural task is known, this task can serve as a 'functional' probe to position the coil for the subsequent investigation of another task (e.g., Gobel et al., 2001; Ro et al., 1999). Such 'hunting' procedures can, however, be time-consuming due to the fact that different locations need to be tested by trial-and-error. Furthermore, the interpretation of the results with respect to brain anatomy is limited by the fact that the coil position was determined functionally and not anatomically. The placing of fiducial markers visible in MRI may help to verify the coil position post hoc. On the other hand, functional, i.e. success-oriented, approaches are generally independent from the uncertainty of the real physical site of stimulation in the tissue (Wagner et al., 2007; in press). Furthermore, functional approaches are not compromised by the discrepancy between anatomical labels and functional neuroanatomy resulting from the fact that the correlation between macroscopic features (e.g., gyri, sulci) and the functional subdivisions of the cortex (e.g., Brodmann areas) may vary considerably between regions (Brett et al., 2002).

Likewise, SNS have been used with different options: first, the gross anatomy of the cerebral cortex itself may serve as a reference system. However, reliable anatomical landmarks exist for very few target sites and individual differences of gyral folding and cortical layering have to be acknowledged. The functional identification of a brain area with SNS requires that the same individual participates in both the fMRI and TMS study. Positioning of the coil over the local maximum of the fMRI activation cluster no longer assumes a fixed relationship between anatomical landmarks and task-related functional activations. However, reliable fMRI activations can often not be obtained at the single-subject level. Alternatively, functional neuroimaging data obtained from the literature can be used for navigation ("probabilistic approach"; Paus et al., 1997). This approach takes advantage of a relatively high consistency in the location of task-related "activations" across individuals. One disadvantage of this method is, however, that it requires some computational steps to transfer the group-based information back into the subject's "native" MRI space (for details, see Paus et al., 1997; Sparing et al., 2008). Since such a procedure is imperfect *per se*, the choice of the appropriate mathematical algorithms and head models should be carried out with great care. Importantly, two recent evaluations of different stereotaxic navigation strategies clearly proved their superiority against common procedures based on functional guidance or the 10/20 EEG system (Sack et al., in press; Sparing et al., 2008).

Target definition II – scalp vs. cortex

A key problem of most localization approaches is the assumption that a ‚cortical' area is targeted best by the alignment of the coil to the closest projected point on the subject's scalp. Using the 10-20 EEG system the coil is, for instance, placed above a point marked on the scalp assuming that this position lies orthogonal in shortest distance to the real ‚cortical' target. It is obvious that this procedure depends upon on the correct orientation of the coil axis and that, in addition to errors in positioning, errors in orientation will add to the overall error in hitting the actual target in the cortex. In contrast, the MRI-guided SNS allows to target cortical targets directly taking adjustments in coil position as well as orientation into account.

Coil monitoring – intermittent vs. continuous

Since TMS experiments are usually conducted in blocks lasting from minutes to hours, the coil needs to be either locked in place or repositioned between blocks. Even the use of mounting devices cannot prevent small drifts of the coil or the subject. From this it is obvious that registration of the coil position as offered by most SNS should be continuous for highest accuracy. Thus, even small errors in positioning can inherently be corrected by adjustments in coil position or orientation.

Conclusion

In summary, as outlined above, the use of frameless stereotaxic neuronavigation systems provides clear advantages. Function-guided localization may represent an alternative option. 'Scalp surface based approaches' such as the 10-20 EEG system should, however, only be applied in situations, which do not necessitate high spatial precision. SNS only allows for the precise monitoring of the TMS coil with respect to all degrees of freedom and online control, which is indispensable for studies applying TMS over a longer period of time. Modern software interfaces also incorporate online recording of the exact TMS stimulus location and dose calculations. Case histories and aiming tools help to apply the next stimulus taking into account the parameters of the preceding stimulus. However, the systems still ignore the electromagnetic interaction between the stimulating fields and the actual tissues that comprise the physical site of stimulation (Miranda et al., 2003; Wagner et al., 2006, in press). In the future, the incorporation of computer-modeling of the stimulation current distribution derived from anatomical MRI scans may help to further refine this methodology. Likewise, the development of mechanical (automatic) positioning aids may help to increase accuracy and reproducibility of stereotaxic coil positioning (Lancaster et al., 2004).

Until then, other methodological problems remain to be solved, e.g., the impact of the scalp-to-cortex distance (Stokes et al., 2007), the influence of the current orientation induced by TMS (Fox et al., 2004; Hill et al., 2000) and the exact physical site of stimulation (Rushworth & Taylor, 2006; Wagner et al., 2007, in press). Further methodological advances may be expected from MR-compatible TMS systems allowing TMS application inside the scanner without an error-prone coregistration procedure (e.g., Bestmann et al., 2003, in press; Bohning et al., 2003).

References

Bestmann S, Baudewig J, Frahm J. On the synchronization of transcranial magnetic stimulation and echo-planar imaging. *Journal of Magnetic Resonance Imaging*, 17: 309-317, 2003.

Bohning DE, Denslow S, Bohning PA, Walker JA, George MS. A TMS coil positioning/holding system for MR image-guided TMS interleaved with fMRI. *Clinical Neurophysiology*, 114: 2210-2219, 2003.

Brett M, Johnsrude IS, Owen AM. The problem of functional localization in the human brain. *Nature Reviews Neuroscience*, 3: 243-249, 2002.

Fox PT, Narayana S, Tandon N, Sandoval H, Fox SP, Kochunov P, Lancaster JL. Column-based model of electric field excitation of cerebral cortex. *Human Brain Mapping*, 22: 1-14, 2004.

Lancaster JL, Narayana S, Wenzel D, Luckemeyer J, Roby J, Fox P. Evaluation of an image-guided, robotically positioned transcranial magnetic stimulation system. *Human Brain Mapping*, 22: 329-340, 2004.

Gobel S, Walsh V, Rushworth MF. The mental number line and the human angular gyrus. *Neuroimage*, 14: 1278-1289, 2001.

Herwig U, Padberg F, Unger J, Spitzer M, Schonfeldt-Lecuona C. Transcranial magnetic stimulation in therapy studies: examination of the reliability of "standard" coil positioning by neuronavigation. *Biological Psychiatry*, 50: 58-61, 2001.

Herwig U, Satrapi P, Schonfeldt-Lecuona C. Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. *Brain topography*, 16: 95-99, 2003.

Hill AC, Davey NJ, Kennard C. Current orientation induced by magnetic stimulation influences a cognitive task. *Neuroreport*, 11: 3257-3259, 2000.

Miranda PC, Hallett M, Basser PJ. The electric field induced in the brain by magnetic stimulation: a 3-D finite-element analysis of the effect of tissue heterogeneity and anisotropy. *IEEE Transactions on Biomedical Engineering,* 50: 1074-1085, 2003.

Neggers SF, Langerak TR, Schutter DJ, Mandl RC, Ramsey NF, Lemmens PJ, Postma A. A stereotactic method for image-guided transcranial magnetic stimulation validated with fMRI and motor-evoked potentials. *Neuroimage*, 21: 1805-1817, 2004.

Okamoto M, Dan H, Sakamoto K, Takeo K, Shimizu K, Kohno S, Oda I, Isobe S, Suzuki T, Kohyama K, Dan I. Three-dimensional probabilistic anatomical cranio-cerebral correlation via the international 10-20 system oriented for transcranial functional brain mapping. *Neuroimage*, 21: 99-111, 2004.

Paus T. Imaging the brain before, during, and after transcranial magnetic stimulation. *Neuropsychologia*, 37: 219-224, 1999.

Paus T, Jech R, Thompson CJ, Comeau R, Peters T, Evans AC. Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. *Journal of Neuroscience*, 17: 3178-3184, 1997.

Ro T, Cheifet S, Ingle H, Shoup R, Rafal R. Localization of the human frontal eye fields and motor hand area with transcranial magnetic stimulation and magnetic resonance imaging. *Neuropsychologia*, 37: 225-231, 1999.

Ruff CC, Driver J, Bestmann S. Combining TMS and fMRI: From 'virtual lesions' to functional-network accounts of cognition. *Cortex*, in press. Epub ahead of print, doi:10.1016/j.cortex.2008.10.012.

Rushworth MF, Taylor PC. TMS in the parietal cortex: updating representations for attention and action. *Neuropsychologia*, 44: 2700-2716, 2006.

Sack AT, Kadosh RC, Schuhmann T, Moerel M, Walsh V, Goebel R. Optimizing Functional Accuracy of TMS in Cognitive Studies: A Comparison of Methods. *Journal of Cognitive Neuroscience*, in press. Epub ahead of print, doi: 10.1162/jocn.2009.21126.

Schonfeldt-Lecuona C, Thielscher A, Freudenmann RW, Kron M, Spitzer M, Herwig U. Accuracy of stereotaxic positioning of transcranial magnetic stimulation. *Brain topography*, 17: 253-259, 2005.

Sparing R, Buelte D, Meister IG, Paus T, Fink GR. Transcranial magnetic stimulation and the challenge of coil placement: a comparison of conventional and stereotaxic neuronavigational strategies. *Human Brain Mapping*, 29: 82-96, 2008.

Stokes MG, Chambers CD, Gould IC, English T, McNaught E, McDonald O, Mattingley JB. Distance-adjusted motor threshold for transcranial magnetic stimulation. *Clinical Neurophysiology*, 118: 1617-1625, 2007.

Wagner T, Fregni F, Eden U, Ramos-Estebanez C, Grodzinsky A, Zahn M, Pascual-Leone A. Transcranial magnetic stimulation and stroke: a computer-based human model study. *Neuroimage*, 30: 857-870, 2006.

Wagner T, Rushmore J, Eden U, Valero-Cabre A. Biophysical foundations underlying TMS: Setting the stage for an effective use of neurostimulation in the cognitive neurosciences. *Cortex*, in press. Epub ahead of print, doi:10.1016/j.cortex.2008.10.002.

Wagner T, Valero-Cabre A, Pascual-Leone A. Noninvasive human brain stimulation. *Annual Review of Biomedical Engineering*, 9: 527-565, 2007.

Zinreich SJ, Tebo SA, Long DM, Brem H, Mattox DE, Loury ME, vander Kolk CA, Koch WM, Kennedy DW, Bryan RN. Frameless stereotaxic integration of CT imaging data: accuracy and initial applications. *Radiology*, 188: 735-742, 1993.