

Positional paper

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

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5 **Neuronavigation for transcranial magnetic stimulation (TMS):**  
6 **where we are and where we are going.**  
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20 *Short title:* Navigation for TMS.

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22 *Key words:* image-guided TMS; frameless stereotaxy; TMS aiming accuracy; rTMS; precision;  
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24 stereotactic space; noninvasive brain stimulation.  
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1 Focal TMS is an excellent neurophysiological tool for studying basic motor as well as higher cognitive  
2 brain functions. In brain mapping studies using TMS, the precise and accurate positioning of the TMS  
3 coil over the targeted cortical site represents one of the most challenging aspects of the experimental  
4 procedure. Exact coil positioning is crucial for the correct interpretation of stimulation effects. TMS  
5 studies of higher cognitive functions may, however, display high inter-subject and between-group  
6 variability, since sulcal anatomy, cytoarchitecture and function do not correlate well in many brain  
7 areas (Brett et al., 2002). In this case, a clear strategy how to localize the target area as well as how to  
8 position precisely the TMS coil is indispensable. In the following, we delineate the key problems of  
9 neuronavigation for TMS and how they can be addressed by modern neuronavigational strategies:  
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#### 22 *Reference frame – group-based vs. individualised*

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24 Successful neuronavigation for TMS requires careful consideration of interindividual anatomical  
25 variability, in particular in case of target areas with large intersubject variability such as the prefrontal  
26 cortex or along the interparietal sulcus. For instance, the 10-20 EEG electrode system is based on the  
27 rough assumption that there is a consistent correlation between scalp locations and underlying brain  
28 structures across subjects. However, skull deformities as well as interindividual variability of the  
29 cerebral sulci may lead to variations of up to 20 mm in the different axes, with some electrode  
30 positions being associated with larger variability than others (Herwig et al., 2003; Okamoto et al.,  
31 2004). Another commonly used positioning strategy draws upon a reference point at which TMS  
32 directly elicits an objective response, e.g., muscle twitches (M1). Other brain areas are subsequently  
33 located in spatial relation to this reference point. Accuracy is likely to fall off with increasing distance:  
34 Whereas areas adjacent to M1, e.g., S1, can be determined with reasonable accuracy, the identification  
35 of more distantly located sites, e.g., in the frontal cortex, is less reliable (Herwig et al., 2001).  
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51 To better account for interindividual anatomical differences, image-guided frameless stereotaxic  
52 neuronavigation systems (SNS) have been developed for the use with TMS (e.g., Schoenfeldt-Lecuona  
53 et al., 2005; Wagner et al., 2007; Sparing et al., 2008). SNS use the subject's individual MRI for  
54 navigation via a subject-image coregistration procedure based on facial/cranial landmarks. Although  
55 the system's precision relies upon technical limitations, the quality of the MRI investigation and exact  
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1 coregistration, the spatial deviations have been shown to lie within the millimeter range (Neggers et  
2 al., 2004; Schonfeldt-Lecuona et al., 2005).

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6 *Target definition I – anatomical vs. functional*

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

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40 Likewise, SNS have been used with different options: first, the gross anatomy of the cerebral cortex  
41 itself may serve as a reference system. However, reliable anatomical landmarks exist for very few  
42 target sites and individual differences of gyral folding and cortical layering have to be acknowledged.  
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1 this method is, however, that it requires some computational steps to transfer the group-based  
2 information back into the subject's "native" MRI space (for details, see Paus et al., 1997; Sparing et  
3 al., 2008). Since such a procedure is imperfect *per se*, the choice of the appropriate mathematical  
4 algorithms and head models should be carried out with great care. Importantly, two recent evaluations  
5 of different stereotaxic navigation strategies clearly proved their superiority against common  
6 procedures based on functional guidance or the 10/20 EEG system (Sack et al., in press; Sparing et al.,  
7 2008).

#### 17 *Target definition II – scalp vs. cortex*

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

#### 39 *Coil monitoring – intermittent vs. continuous*

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

### 55 **Conclusion**

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

13 Until then, other methodological problems remain to be solved, e.g., the impact of the scalp-to-cortex  
14 distance (Stokes et al., 2007), the influence of the current orientation induced by TMS (Fox et al.,  
15 2004; Hill et al., 2000) and the exact physical site of stimulation (Rushworth & Taylor, 2006; Wagner  
16 et al., 2007, in press). Further methodological advances may be expected from MR-compatible TMS  
17 systems allowing TMS application inside the scanner without an error-prone coregistration procedure  
18 (e.g., Bestmann et al., 2003, in press; Bohning et al., 2003).

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