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Methods for estimating cortical motor representation size and location in navigated transcranial magnetic stimulation

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HIGHLIGHTS

- Navigated transcranial magnetic stimulation (nTMS) can outline cortical motor areas.
- Novel methods were implemented for assessing muscle representation areas with nTMS.
- Hand muscle representation can be located with high repeatability.
- Spline interpolation method was found most suitable for estimating motor area size.
- Spline interpolation and Voronoi tessellation can assess motor area size and location.

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ABSTRACT

Background: Navigated transcranial magnetic stimulation (nTMS) is used for locating and outlining cortical representation areas, e.g., of motor function and speech. At present there are no standard methods of measuring the size of the cortical representation areas mapped with nTMS. The aim was to compare four computation methods for estimating muscle representation size and location for nTMS studies.
New method: The motor cortex of six subjects was mapped to outline the motor cortical representation of hand muscles. Four methods were compared to assess cortical representation size in nTMS. These methods included: (1) spline interpolation method, (2) convex hull method, which outlines all positive motor responses, (3) Voronoi tessellation method, which assigns a specific cortical area for each stimulus location, and (4) average point-area method, which computes an average representation area for each stimulus with the assumption of evenly spaced stimulus locations, i.e., the use of a grid.
Results: All applied methods demonstrated good repeatability in measuring muscle representation size and location, while the spline interpolation and the convex hull method demonstrated systematically larger representation areas ($p < 0.05$) as compared to the average point-area method. Spline interpolation method demonstrated the best repeatability in location.
Comparison with existing methods: Unlike the previous methods, the presented methods can be applied for the estimation of the representation area of nTMS-induced activation without the use of an evenly spaced stimulus grid.
Conclusions: The spline interpolation method and the Voronoi tessellation method could be used for evaluating motor cortical muscle representation size and location with nTMS, e.g., to study cortical plasticity.

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1. Introduction

Navigated transcranial magnetic stimulation (nTMS) combines conventional magnetic stimulation and neuronavigation. One of its applications is to locate and outline the representation areas of speech, visual cortex and motor function (Freund et al., 2011; Krings et al., 2001; Lioumis et al., 2012; Picht et al., 2009; Salminen-Vaparanta et al., 2012; Sollmann et al., 2013). Outlining muscle representation areas has proved useful in presurgical evaluations (Krieg et al., 2012; Paiva et al., 2012; Picht et al., 2011; Tarapore et al., 2012). In addition, nTMS has been applied to estimate the size of the cortical representations (Foltys et al., 2003; Labyt et al., 2007; Marconi et al., 2007; Vaalto et al., 2011). The motor areas have also

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been assessed through centre of gravity (CoG) which represents a spatial average of the corticomotor representation (Borghetti et al., 2008; Byrnes et al., 1998; Classen et al., 1998; Freund et al., 2011; Uy et al., 2002; Wassermann et al., 1992; Wilson et al., 1993). CoGs may be used to detect shifts in the cortical representation areas (Byrnes et al., 1998; Siebner and Rothwell, 2003). The CoG considers the entire map of responses to evaluate the representation location, unlike the alternative, the "hotspot", which represents the location of maximal activation, and neglects the surrounding cortical areas. Therefore, the CoG can be used to detect shifts in the response map distribution, which may not affect the site of maximum activation (Siebner and Rothwell, 2003). In addition, CoG has been shown to be more stable than the hotspot (Weiss et al., 2013). However, when using CoG, in principle a cortical representation area may be located in an area, which produces low or no responses. Therefore, CoG should be considered a tool for analysis rather than a tool for targeting TMS.

Even though nTMS enables stimulation of distinct cortical structures, it has been a challenge to evaluate the size of the true stimulated cortical area. Past attempts to quantify size of the representation areas have utilized an evenly spaced stimulus grid and have then either counted the number of active locations on the grid or have computed a volume map by summing up all stimulus responses (Foltys et al., 2003; Gagne et al., 2011; Hetu et al., 2011; Kesar et al., 2012; Malcolm et al., 2006; Pascual-Leone et al., 1995; Triggs et al., 1999; Wassermann et al., 1992). These approaches possess the limitation of having to perform the nTMS mapping with evenly spaced stimulus locations to avoid bias in any cortical areas due to denser stimulus spacing. However, they can be used to evaluate the size of the functional cortical area by computing the average point-area of each stimulus location (element) on the grid and then multiplying that with the number of active locations.

One potential method for estimating location and size of a representation area without utilizing a stimulation grid is the spline interpolation method (Borghetti et al., 2008). Spline interpolation method is able to "homogenize" the stimulus spacing to a very small grid. Interpolation method has the downside of potentially altering the original measurement data. Another method utilizing convex hull was recently used to outline the stimulated cortical locations and to estimate the size of the motor area (Vaalto et al., 2011). The convex hull method assumes that the representation area is within a single cluster of stimulus locations in the cortex which produce a response, and therefore it utilizes only positive responses, and not the negative ones. One potential method, not yet applied with nTMS, is Voronoi tessellation method, which may be used to estimate the cortical representation area. This method considers not only the stimulated cortical location, but its relation to surrounding stimulation locations. Like spline interpolation method, Voronoi tessellation method does not assume that a single cluster of stimuli outlines a representation area, agreeing with experimental findings (Donoghue et al., 1992). Neither spline interpolation method nor the Voronoi tessellation methods have the strict requirement of evenly spaced stimulation locations, and therefore the use of a stimulus grid is not essential.

The methods evaluated in this study are straightforward and easily applicable with nTMS, and therefore have great potential and allow for quantitative evaluation of cortical representation areas through measurement of the area where TMS must be focused in order to induce a response. For this purpose, I compare different methods for estimation of motor representation size and location. One of the key applications in the future of nTMS is the scientific and clinical evaluation of the plastic changes of the motor cortex in stroke, pain, and brain tumour patients. The present study aims in providing a suitable method for such application.

2. Methods

2.1. Subjects

Six healthy subjects (5 right-handed, 1 left-handed, age 23–29 years, 4 female) were recruited for this study. The head of each subject was imaged using 3T MRI scanner (Philips Medical Systems, Eindhoven, The Netherlands) with T1-weighted 3D sequence with $1 \times 1 \times 1$ mm voxel size. One brain tumour patient (48-year-old, right-handed male) was imaged with a similar sequence using 1.5T MRI scanner (Siemens, Erlangen, Germany) for the demonstration of the application with clinical patients. The images were utilized with nTMS. The study was conducted using eXimia TMS stimulator and figure-of-eight coil with biphasic pulse waveform (Nexstim Oy, Helsinki, Finland). During the nTMS-experiment, electromyography (EMG) was recorded with integrated eXimia EMG. EMG was monitored and visualized to the subjects/patient as muscle activity feedback during the experiments to be able to stimulate relaxed muscles. Motor evoked potentials (MEPs) were analyzed as peak-to-peak amplitudes from stimulus-locked EMG responses.

2.2. Experimental protocol

The primary motor cortex on both hemispheres was initially mapped for the optimal stimulus site of the right hand abductor pollicis brevis (APB) muscle using nTMS. During the mapping, the TMS coil was oriented with respect to cortical anatomy so that the induced electric field was perpendicular to the closest sulcus (Fig. 1). Then, optimal coil orientation was fine-tuned by rotating the coil at the stimulus site to maximize the MEP amplitude (Julkunen et al., 2009). Subsequently, the resting motor threshold (rMT) for the APB muscle was determined at the optimal stimulation site by using the Motor Threshold Assessment Tool (MTAT 2.0) with 20–30 stimuli (Awiszus, 2003; Awiszus and Borckardt, 2012). A motor response of $\geq 50\,\mu V$ in amplitude was accepted as a MEP. Then, the vicinity of the optimal stimulation location site was mapped at stimulation intensity (SI) of 110% of rMT (Pascual-Leone et al., 1995) separately with and without the aid of a grid tool available in eXimia software (version 3.2.2) (Fig. 1). The stimulus locations were visualized and projected to a surface which was chosen based on cortical anatomy to be the outermost surface where the grey and white matter were distinguishable (Niskanen et al., 2010). During the mapping procedure, EMG was measured from the APB and abductor digiti minimi (ADM) muscle of the contralateral hand. The mapping was continued in all directions until mapped area was outlined with locations producing negative responses, i.e., no MEP was observed. The mapping procedure was conducted twice; once with the aid of the stimulation grid and once without. The order of the two was randomized. The representation area and CoGs of both recorded muscles were estimated separately.

2.3. Computation of representation area

The assumption was made that the TMS coil stimulates the area of the cortex closest to the coil, and therefore the cortical representation area of a muscle was simplified to a surface following the shape of the head. It was also assumed that the stimulating electric field is similar in all stimulus locations, and variations in the stimulating cortical electric field do not induce variation to the induced MEPs. Hence, to compute the surface area of the cortical representation areas, the original stimulus locations were first transformed from 3D to 2D by fitting an ellipsoid to the cortical stimulation locations, and utilizing singular value decomposition for the transform function. The mean distance between the closest neighbouring points changed <0.7% during the coordinate transform, therefore making the transforming

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