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Localization of cortical primary motor area of the hand using navigated transcranial magnetic stimulation, BOLD and arterial spin labeling fMRI

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HIGHLIGHTS

- The congruence between BOLD and ASL fMRI and nTMS was good in motor mapping.
- The BOLD fMRI motor task had little impact on the measured motor representation.
- TMS induced silent periods were a feasible motor mapping method.

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ABSTRACT

Background: Although the relationship between neuronavigated transcranial magnetic stimulation (nTMS) and functional magnetic resonance imaging (fMRI) has been widely studied in motor mapping, it is unknown how the motor response type or the choice of motor task affect this relationship.
New method: Centers of gravity (CoGs) and response maxima were measured with blood-oxygen-level dependent (BOLD) and arterial spin labeling (ASL) fMRI during motor tasks against nTMS CoGs and response maxima, which were mapped with motor evoked potentials (MEPs) and silent periods (SPs).
Results: No differences in motor representations (CoGs and response maxima) were observed in lateral-medial direction ($p = 0.265$). fMRI methods localized the motor representation more posterior than nTMS ($p < 0.001$). This was not affected by the BOLD fMRI motor task ($p > 0.999$) nor nTMS response type ($p > 0.999$). ASL fMRI maxima did not differ from the nTMS nor BOLD fMRI CoGs ($p \geq 0.070$), but the ASL CoG was deeper in comparison to other methods ($p \leq 0.042$). The BOLD fMRI motor task did not influence the depth of the motor representation ($p \geq 0.745$). The median Euclidean distances between the nTMS and fMRI motor representations varied between 7.7 mm and 14.5 mm and did not differ between the methods ($F \leq 1.23$, $p \geq 0.318$).
Comparison with existing methods: The relationship between fMRI and nTMS mapped excitatory (MEP) and inhibitory (SP) responses, and whether the choice of motor task affects this relationship, have not been studied before.
Conclusions: The congruence between fMRI and nTMS is good. The choice of nTMS motor response type nor BOLD fMRI motor task had no effect on this relationship.

Abbreviations: AC-PC, anterior commissure-posterior commissure; ADM, abductor digiti minimi; APB, abductor pollicis brevis; ASL, arterial spin labeling; ASL_{wiggle}, arterial spin labeling contrast of finger wiggle; BOLD, blood-oxygen-level dependent; $BOLD_{squeeze}$, blood-oxygen-level dependent contrast of hand squeeze; $BOLD_{wiggle}$, blood-oxygen-level dependent contrast of finger wiggle; CoG, center of gravity; EMG, electromyography; FDI, first dorsal interosseous; fMRI, functional magnetic resonance imaging; FWHM, full-width at half maximum; GLM, general linear model; MEP, motor evoked potential; MEP_{CoG}, center of gravity calculated from the motor evoked potential amplitudes; MEP_{max}, response maximum calculated from the motor evoked potential amplitudes; MSO, maximum stimulator output; MTAT, Motor Threshold Assessment Tool; nTMS, neuronavigated transcranial magnetic stimulation; rMT, resting motor threshold; SP, silent period; SP_{CoG}, center of gravity calculated from the silent period durations; SP_{max}, response maximum calculated from the silent period durations; SPT30, stimulation threshold for an SP duration of 30 ms.

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1. Introduction

Primary motor area, presumably located in the precentral gyrus (Yousry et al., 1997), is involved in producing muscle activity and muscle movement (Kakei et al., 1999). Commonly, the motor area is characterized by its location and size. Several neurological diseases, such as brain tumors and traumas as well as motor training may relocate the motor area even to unexpected locations from the precentral gyrus, and expand or reduce its size (Fandino et al., 1999; Liepert et al., 2000a; Mäkelä et al., 2013; Netz et al., 1997; Vaalto et al., 2013). Furthermore, the excitability of the motor areas might change (Jussen et al., 2016). Accordingly, in functional motor mapping applications, such as in pre-operative mapping, it is important to apply an accurate and repeatable method to locate the motor areas.

Neuronavigated transcranial magnetic stimulation (nTMS) is a widely used method to assess the functional characteristics of the cortical motor areas. nTMS can be applied to map the motor area by finding the locations producing responses in the contralateral target muscle (Julkunen 2014; Picht et al., 2011). When the target muscles are at rest, nTMS may generate a motor evoked potential (MEP). During voluntary contraction of the target muscles, on the contrary, the stimulation may result in an MEP followed by a silent period (SP). The SP is observed as a temporary cessation of ongoing muscle activity (Fuhr et al., 1991). The MEP is thought to reflect the function of the excitatory motor system, whereas the SP is considered to originate from the activation of the inhibitory system (Rossini et al., 2015). Thereby, nTMS is able to evaluate the characteristics of the excitatory and inhibitory systems separately if the evoked motor response type is varied.

The conventional approach in nTMS motor mapping is to apply the resting MEP amplitudes to evaluate the cortical motor area (Kallioniemi and Julkunen, 2016; Picht et al., 2011; Takahashi et al., 2013). This MEP mapping procedure has been validated against the invasive direct cortical stimulation (Picht et al., 2011; Vitikainen et al., 2013), which is recognized as the gold standard in functional mapping. Earlier, SPs have also been used for localizing the motor area in a few studies (Mäkelä et al., 2013; Pitkänen et al., 2015; Wassermann et al., 1993; Wilson et al., 1993). SPs can be induced with slightly lower stimulation intensities than resting MEPs (Kallioniemi et al., 2014), enabling mapping even in cases when resting MEPs cannot be evoked (Mäkelä et al., 2013). Cortical motor areas measured with SPs have been demonstrated to slightly differ from those where MEPs were used (Pitkänen et al., 2015; Wassermann et al., 1993; Wilson et al., 1993). Therefore, it is plausible that the motor areas consist of both excitatory and inhibitory components which might have slightly different cortical topographies.

The cortical motor areas can also be located with functional magnetic resonance imaging (fMRI) during a motor task. The most commonly used fMRI technique is blood-oxygen-level dependent (BOLD) contrast which is routinely applied for functional mapping of motor, language and visual areas (Drobyshevsky et al., 2006). The BOLD signal measures the neural activity indirectly via neurovascular coupling from changes in blood flow, blood volume and consumption of oxygen (Kwong et al., 1992; Mandeville et al., 1999; Ogawa et al., 1993). The functional contrast can be acquired as these blood related changes modify the local concentration of deoxygenated hemoglobin which, due to its paramagnetic properties, distorts the local magnetic field (Thulborn et al., 1982).

An alternative to BOLD contrast in functional motor mapping is arterial spin labeling (ASL) fMRI which utilizes magnetically labeled arterial blood water as a magnetic tracer (Detre et al., 1992; Williams et al., 1992). ASL provides a direct measure of arterial blood perfusion (Silva et al., 1997) which refers to the delivery of oxygen and nutrients into the tissue. The perfusion measures in ASL are derived from pairwise subtraction of temporally consecutive images of with and without blood labeling. Due to this, baseline drift and motion related artefacts are efficiently reduced compared to BOLD fMRI (Aguirre et al., 2002 Wong, 1999). There are also some indications that ASL might outperform BOLD in spatial resolution with neuronal activity (Duong et al., 2001; Silva et al., 1999). ASL is not, however, as extensively used as BOLD for fMRI, since it is more challenging to implement, has a considerably lower signal change during neural activation, is a slower imaging method due to pairwise subtraction of images and is still very limited in terms of availability.

The spatial agreement between fMRI and nTMS is important in motor mapping applications, as both of these methods are commonly used to complement each other to gain more confidence in the mapping result. Further, the methods have been combined in fMRI-informed nTMS experiments where nTMS targets have been based on the fMRI activation site (Beauchamp et al., 2010; Reichenbach et al., 2011). Several studies exist which evaluate the discrepancy between nTMS and BOLD fMRI mapped motor areas (Bastings et al., 1998; Diekhoff et al., 2011; Herwig et al., 2002). These studies have concluded that the cortical motor areas mapped with nTMS induced MEPs are slightly more anterior than those acquired with fMRI and that the mean Euclidean distance between the response-weighted center of the motor areas measured with these methods is from a few millimetres up to about two centimetres (Bastings et al., 1998; Diekhoff et al., 2011; Herwig et al., 2002). Only one study has compared the motor areas mapped with nTMS induced MEPs with ASL fMRI in addition to BOLD fMRI (Diekhoff et al., 2011). It investigated the motor areas on the dominant, left hemisphere by using a single motor task, and found that the choice of fMRI method (BOLD/ASL) does not influence the congruence between fMRI and nTMS in the anterior-posterior direction.

In our previous study (Pitkänen et al., 2015), we observed that the nTMS motor areas of small, separate hand muscles mapped with MEPs were more anterior than those mapped with SPs. This implies that a better congruence between fMRI and nTMS might be achieved when using SPs as the nTMS motor response type in comparison to MEPs. Thereby, considering the findings of our previous study and that of Diekhoff et al. (2011), the aim of the present study was to extend the comparison between fMRI and nTMS. We evaluated the congruence between different fMRI techniques and motor tasks with nTMS in localizing the cortical motor representations by using two motor response types. These motor responses were MEPs, which reflect the excitatory properties of the motor cortex and SPs which are linked to the inhibitory system. Our specific aims were to evaluate (1) does the choice of motor task affect the comparison between BOLD fMRI and nTMS mapped motor areas, (2) does the choice of nTMS motor response type affect the congruence between fMRI and nTMS mapped motor areas, and (3) are SPs a feasible motor response type to be applied in nTMS motor mapping.

2. Materials and methods

2.1. Subjects

We recruited 10 healthy right-handed volunteers (5 females, 5 males, age range 21–32 years). Written informed consent was collected from all the subjects and the study was approved by the local ethics council (permission 1/2014). All the subjects were eligible for magnetic resonance imaging (MRI) (Shellock and Spinazzi, 2008) and nTMS (Rossi et al., 2009), and none had a history of neurological disorders. The study included an fMRI (BOLD and ASL) and an nTMS motor mapping (with MEPs and SPs as the motor response