Parcellation of the human sensorimotor cortex: a resting-state fMRI study

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The sensorimotor cortex is a brain region comprising the primary motor cortex (MI) and the primary somatosensory (SI) cortex. In humans, investigation into these regions suggests that MI and SI are involved in the modulation and control of motor and somatosensory processing, and are somatotopically organized according to a body plan (Penfield & Boldrey, 1937). Additional investigations into somatotopic mapping in relation to the limbs in the peripheral nervous system and SI in central nervous system have further born out the importance of this body-based organization (Wall & Dubner, 1972). Understanding the nature of the sensorimotor cortex's structure and function has broad implications not only for human development, but also motor learning (Taubert *et al.*, 2011) and clinical applications in structural plasticity in Parkinson's disease (Sehm *et al.*, 2014), among others.

The aim of the present thesis is to identify functionally meaningful subregions within the sensorimotor cortex via parcellation analysis. Previously, cerebral subregions were identified in postmortem brains by invasive procedures based on histological features (Brodmann, 1909; Vogt. & Vogt., 1919; Economo, 1926; Sanides, 1970). One widely used atlas is based on Brodmann areas (BA). Brodmann divided human brains into several areas based on the visually inspected cytoarchitecture of the cortex as seen under a microscope (Brodmann, 1909). In this atlas, BA 4, BA 3, BA 1 and BA 2 together constitute the sensorimotor cortex (Vogt. & Vogt., 1919; Geyer *et al.*, 1999; Geyer *et al.*, 2000).

However, BAs are incapable of delineating the somatotopic detail reflected in other research (Blankenburg *et al.*, 2003). And, although invasive approaches have proven reliable in the discovery of functional parcellation in the past, such approaches are marked by their irreversibility which, according to ethical standards, makes them unsuitable for scientific inquiry. Therefore, it is necessary to develop non-invasive approaches to parcellate functional brain regions.

In the present study, a non-invasive and task-free approach to parcellate the sensorimotor cortex with resting-state fMRI was developed. This approach used functional connectivity patterns of brain areas in order to delineate functional subregions as connectivity-based parcellations (Wig *et al.*, 2014). We selected two adjacent BAs (BA 3 and BA 4) from a standard template to cover the area along the

central sulcus (Eickhoff *et al.*, 2005). Then subregions within this area were generated using resting-state fMRI data. These subregions were organized somatotopically from medial-dorsal to ventral-lateral (corresponding roughly to the face, hand and foot regions, respectively) by comparing them with the activity maps obtained by using independent motor tasks. Interestingly, resting-state parcellation map demonstrated higher correspondence to the task-based divisions after individuals had performed motor tasks. We also observed higher functional correlations between the hand area and the foot and tongue area, respectively, than between the foot and tongue regions. The functional relevance of those subregions indicates the feasibility of a wide range of potential applications to brain mapping (Nebel *et al.*, 2014).

In sum, the present thesis provides an investigation of functional network, functional structure, and properties of the sensorimotor cortex by state-of-art neuroimaging technology. The methodology and the results of the thesis hope to carry on the future research of the sensorimotor system.

Abbreviations

BA   Brodmann areas

BOLD blood-oxygen level dependent

CS   central sulcus

DWI   diffusion-weighted imaging

FC   functional connectivity

fMRI   functional magnetic resonance imaging

LFF   low frequency fluctuations

MI   the primary motor cortex

MRI   magnetic resonance imaging

rs-fMRI resting-state fMRI

SI   the primary somatosensory cortex

SCA   the seed-based correlation analysis

Chapter 1: Introduction

The sensorimotor system can be divided into two distinct, yet related faculties: the integration and processing of somatosensory information (Riemann & Lephart, 2002), alongside the modulation and control of motor functions (Penfield & Boldrey, 1937). Even after having been investigated for decades, the anatomical and functional characteristics of this system in humans are still not yet fully understood. This is due, in part, to the methodologies that have been used, which tend to be prohibitively invasive for in vivo human experiments, for instance, stimulating the cortical surface with electrical probes or cytoarchitecture examination (Brodmann, 1909; Penfield & Boldrey, 1937; Geyer *et al.*, 1999).

In the present thesis, a non-invasive parcellation of the sensorimotor cortex is introduced, providing a novel approach to developing a more comprehensive, in-vivo understanding of the sensorimotor system in humans.

1.1 The human sensorimotor cortex

Anatomically, the sensorimotor area is located along the central sulcus of the human cerebral cortex (Fig. 1). As the system's functional roles would suggest, the sensorimotor cortex is often divided into two distinct regions: the primary motor cortex (MI), which is located towards the anterior bank to the central sulcus (precentral gyrus) (Campbell, 1905), and the primary somatosensory cortex (SI) located at the posterior bank to the central sulcus (postcentral gyrus), reaching to the postcentral sulcus (Penfield & Boldrey, 1937). Within one widely used cytoarchitecture-based atlas (Brodmann, 1909), MI is found within Brodmann area 4 (BA 4), and SI is found in BAs 1, 2, and 3 (Vogt. & Vogt., 1919). Other investigators have further subdivided BA 3 into BA 3a and BA 3b (Vogt. & Vogt., 1919; Geyer *et al.*, 1999; Geyer *et al.*, 2000) (Fig. 1). It should be noted here, that Kaas and colleagues have argued that only BA 3 should be assigned as primary SI ("SI proper") (Kaas, 1983). For our study here, we chose BA 3 and BA 4 as our "operational definition" of the sensorimotor cortex.
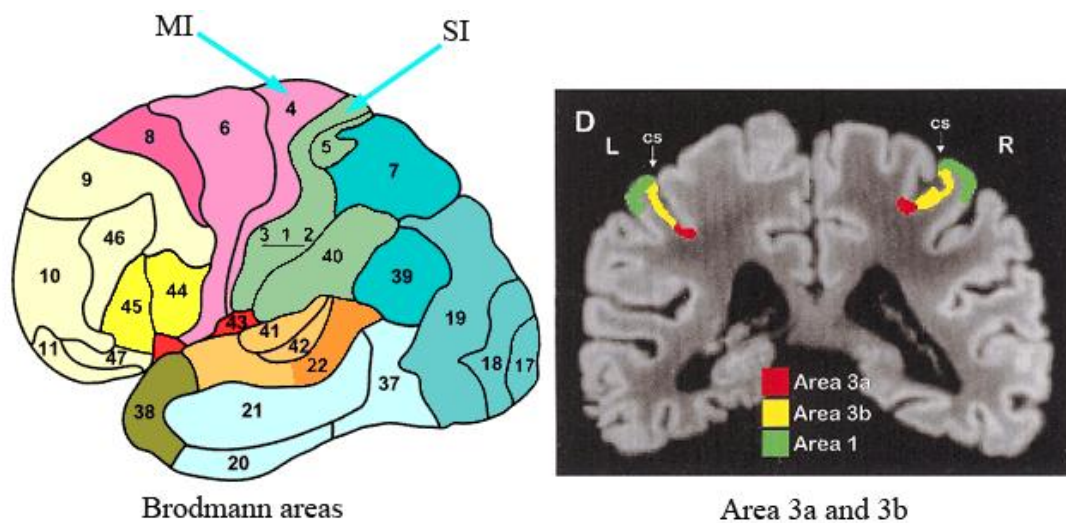
Figure 1. Brodmann areas of the human brain are displayed. Arrows indicate MI and SI, respectively. BA 4 is referred as MI, and BA 3/1/2 are referred as SI. BA 3 is additionally subdivided into BA 3a and BA 3b. The left figure is adapted from the website 'spot.colorado.edu'. The right figure is adapted from Geyer et al., 2000. CS: central sulcus.

An important property of SI and MI relevant to the present thesis is their somatotopic organization (Fig. 2). Several researchers had found that sub-regions related to body-parts are distributed from dorsal to lateral along the central gyrus; for example, cortical areas corresponding to the foot are located superiorly and medially while hand areas are located more laterally (Fig. 2) (Penfield & Boldrey, 1937; Kaas, 1983; Okada *et al.*, 1984). It was this finding that inspired the idea to detect subregions of the sensorimotor area by its functional architecture.
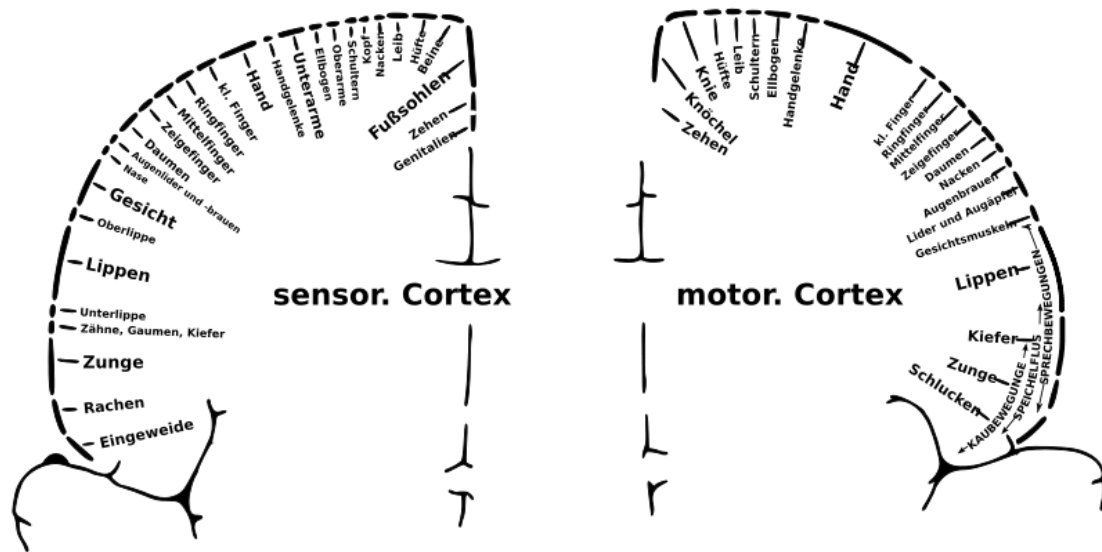
Figure 2. The somatotopic organization of the sensorimotor cortex is presented. SI and MI share very similar organizations. Different areas present the parts of the body and locate from ventral-medial to dorsal-lateral from superior to inferior of the brain. The figure is adapted from the website 'http://en.wikibooks.org/wiki/Consciousness_Studies/The_Neuroscience_Of_Consciousness' and the original book (Penfield. & Rasmussen., 1950).

1.2 Parcellation of the sensorimotor cortex

Generally, parcellation of the cerebral cortex has included examination of its structural properties, functional localization, pathway connections, and topographic mapping (Cohen *et al.*, 2008). One of the oldest and most reliable methods for detecting anatomically and physiologically distinct cortical sub-regions was through physically manipulating the postmortem brain; cutting slices of cortex in order to examine, by microscope, the cytoarchitectures which could be used to delineate different brain regions (Brodmann, 1909; Vogt. & Vogt., 1919; Economo, 1926; Sanides, 1970). While these studies laid the foundation for understanding human brain anatomy, these methods are limited in their ability to reveal the functioning of living brains as these are. These approaches are also, quite obviously, invasive approaches not suitable for studies of living people.

In recent years, non-invasive imaging technology has proven indispensable in advancing our understanding of the living brain, while largely reaffirming the pioneering work of the early neuroanatomists. Using differences, for example, in myelin content and cortical thickness, some borders between Brodmann areas have been identified with high field (e.g. 7 Tesla) magnetic resonance imaging (MRI) (Geyer *et al.*, 2011; Sanchez-Panchuelo *et al.*, 2014). While some structural features can be identified by high field MRI, until recently it was not clear whether the sensorimotor cortex could also be parcellated by resting-state fMRI (rs-fMRI) according to functional features.

1.3 Resting-state fMRI analysis

In the present thesis, resting-state fMRI has been employed to investigate the sensorimotor cortex. While it is just one method available to the fMRI community, rs-fMRI has garnered increasing attention among neuroscientists (Fox & Raichle, 2007) in recent years. This is in part because of the ease with which data can be acquired; participants need not to perform any tasks during scanning, but are rather instructed to remain awake while looking at a fixation screen. The task independent nature of the data, then, allows neuroscientists the potential to use a single data set to test multiple hypotheses. The observation that correlations of low frequency fluctuations (LFF, around 0.01 to 0.08 Hz) of blood-oxygen level dependent (BOLD) signals during task independent scans are statistically significant, as well as physiologically meaningful (Biswal *et al.*, 1995; Cordes *et al.*, 2000), has provided further validation of the method.

1.3.1 Functional connectivity analysis

Functional connectivity (FC) analysis, as developed by Friston and colleagues in 1993, identifies temporal correlation between BOLD signals of two brain regions, and has long been a standard approach to detecting the functional relationships

between different brain regions. Generally, FC analysis is done by a seed-based correlation analysis (i.e., SCA) (Friston *et al.*, 1993; Biswal *et al.*, 1995; Lowe *et al.*, 1998). Brain networks, then, can be detected through the temporal correlation analysis of the BOLD signal between a seed region and other regions in the brain; the regions which show significant temporal correlations with the seed region are considered to belong to the same functional network (Hampson *et al.*, 2002; Greicius *et al.*, 2003; Hampson *et al.*, 2004; Fransson, 2005; Fox & Raichle, 2007).

For instance, when a seed region within the sensorimotor area is selected, the related brain network can be detected by SCA. This approach was widely implemented for detecting changes of brain networks for example due to disease (Li *et al.*, 2002) or stimulations (Hampson *et al.*, 2004). The present thesis will introduce a novel usage of FC analysis.

1.3.2 Connectivity-based parcellation analysis

Connectivity-based parcellation analysis offers a relatively novel, non-invasive approach to identifying anatomically and functionally distinct cortical regions (Fig. 3) (Wig *et al.*, 2014). The central theme is that adjacent voxels, ones which have similar connectivity patterns, should belong to the same subregion. By definition, these regions have a similar function, and so should have similar connectivity patterns as well. Any neuroimaging modalities which can detect connectivity patterns at a millimeter scale are suitable for this analysis. Relevant technologies would then be, for example, diffusion-weighted imaging (DWI) which tracks fiber orientations to detect connectivity of white matter (Johansen-Berg *et al.*, 2004; Anwander *et al.*, 2007; Yu *et al.*, 2011; Liu *et al.*, 2013; Ruschel *et al.*, 2013), and fMRI BOLD signals that can build correlations between voxels (Margulies *et al.*, 2007; Cohen *et al.*, 2008; Margulies *et al.*, 2009; Kim *et al.*, 2010; Li *et al.*, 2013).
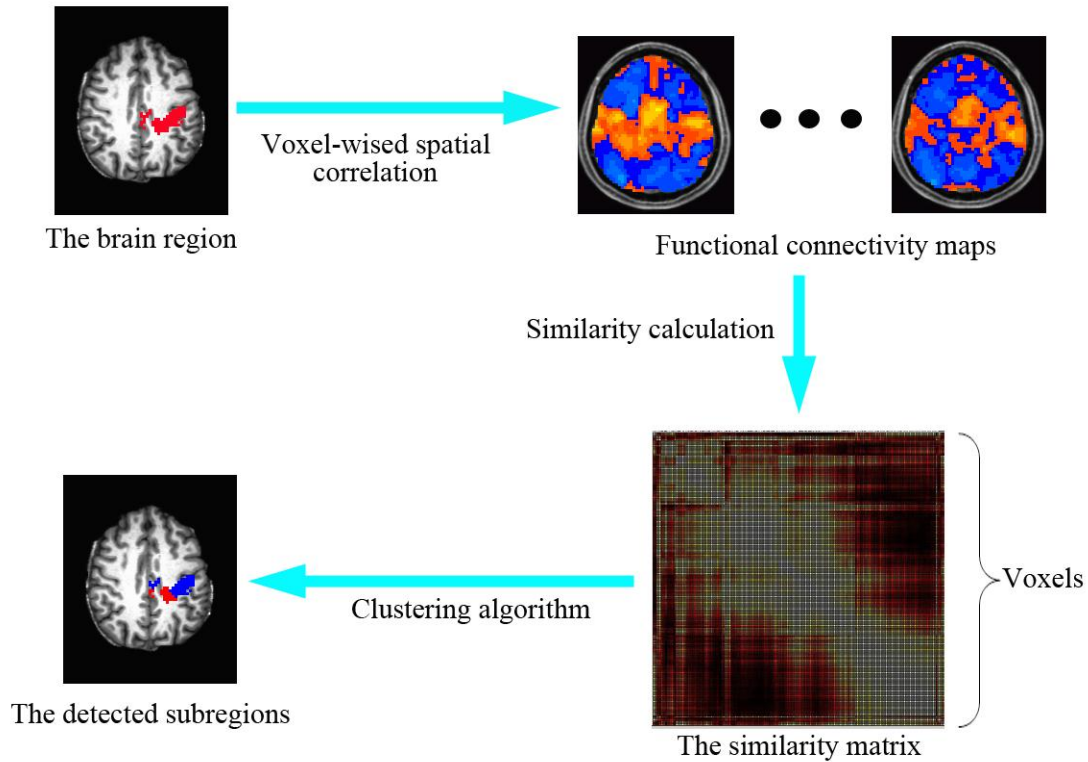
Figure 3. A scheme of connectivity-based parcellation based on fMRI data. The subregions (red and blue color indicates different subregions in the lower left image) can be detected within the selected brain region (red color in the upper left image) through this procedure. All fMRI images are displayed in the axial view.

Rather than performing specific tasks to identify functional subregions, as has traditionally been the case with fMRI data acquisition, resting-state connectivity-based methods provide a task-free and simple approach to address wide ranging scientific topics (Knosche & Tittgemeyer, 2011; Cloutman & Lambon Ralph, 2012; de Reus & van den Heuvel, 2013).

Connectivity-based parcellation with resting-state fMRI data has been widely implemented to parcellate many cerebral regions, for instance, Broca area (Kelly *et al.*, 2010), the primary motor cortex (Gorbach *et al.*, 2011; Nebel *et al.*, 2014), lateral frontal cortex (Goulas *et al.*, 2012), precuneus area (Margulies *et al.*, 2009; Zhang & Li, 2012), lateral parietal cortex (Nelson *et al.*, 2010), anterior cingulate cortex (Margulies *et al.*, 2007), and supplementary motor area (Kim *et al.*, 2010).

Especially relevant to the present thesis, resting-state functional connectivity-based parcellation analysis has already proven to be an effective tool in the detection of subregions within the sensorimotor cortex. The somatotopic organization across bilateral hemispheres within the sensorimotor cortex was confirmed by resting-state functional connectivity analysis (van den Heuvel & Hulshoff Pol, 2010). The voxels which located from dorsal-medial to ventral-lateral along the central sulcus showed one-to-one relationships. Diffusion imaging and resting-state connectivity-based parcellation analysis found four or five subregions within MI or SI (Fig. 4) which visually resemble the body parts distribution expected along central sulcus (Roca *et al.*, 2010). Interestingly, studies have presented similar distributions of activation areas of foot, hand and tongue within the sensorimotor cortex (Buckner *et al.*, 2011; Yeo *et al.*, 2011). It seems that the organization of the connectivity patterns within the sensorimotor cortex correspond more closely to functional features (somatotopy) than cytoarchitectural features (e.g., Brodmann areas).
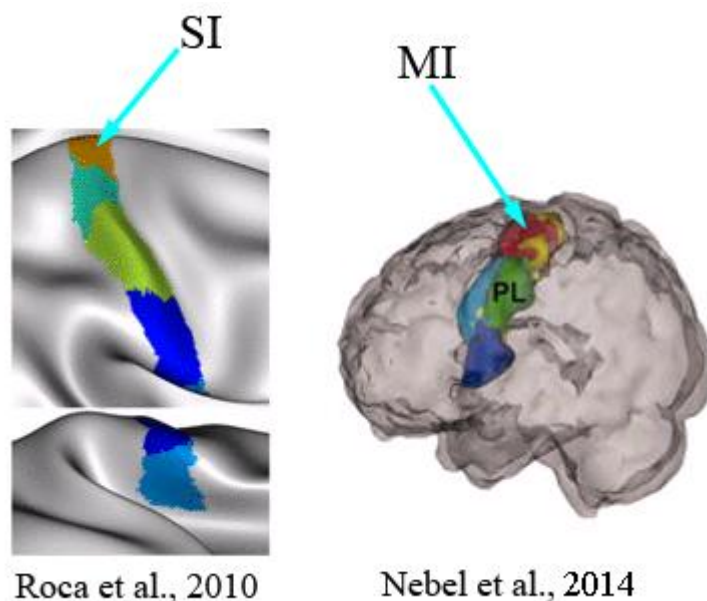

Figure 4. Subregions within MI or SI were identified by previous studies. On the left, results by Roca et al., 2010 which were obtained with DWI are displayed. Different colors indicate the different clusters within SI. On the right results by Nebel et al., 2014 are shown which were obtained with resting state fMRI. Different clusters within MI are indicated by different colors.

Previous studies reported subregions within the sensorimotor cortex based on task-free parcellation, however, they did not provide any validation of the reported (presumable somatotopic) arrangement (e.g., Nebel *et al.*, 2014). The present thesis begins at this juncture: to determine whether the reported subregions discerned through resting-state fMRI data is consistent with the somatotopic arrangement of those body parts. For this purpose, we parcellated the sensorimotor cortex with resting-state fMRI data, then performed an activation-based fMRI during motor tasks in order to obtain cerebral activation areas corresponding to different body parts. We hypothesized that the subregions based on resting-state fMRI data corresponded to the functional somatotopic arrangement as identified by task-based fMRI.

Chapter 2: Publication

Long X, Goltz D, Margulies DS, Nierhaus T, Villringer A. Functional connectivity-based parcellation of the human sensorimotor cortex.

COGNITIVE NEUROSCIENCE

Functional connectivity-based parcellation of the human sensorimotor cortex

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Abstract

Task-based functional magnetic resonance imaging (fMRI) has been successfully employed to obtain somatotopic maps of the human sensorimotor cortex. Here, we showed through direct comparison that a similar functional map can be obtained, independently of a task, by performing a connectivity-based parcellation of the sensorimotor cortex based on resting-state fMRI. Cortex corresponding to two adjacent Brodmann areas (BA 3 and BA 4) was selected as the sensorimotor area. Parcellation was obtained along a medial–lateral axis, which was confirmed to be somatotopic (corresponding roughly to an upper, middle and lower limb, respectively) by comparing it with maps obtained using motoric task-based fMRI in the same participants. Interestingly, the resting-state parcellation map demonstrated higher correspondence to the task-based divisions after individuals performed the motor task. Using the resting-state fMRI data, we also observed higher functional correlations between the centrally located hand region and the other two regions, than between the foot and tongue. The functional relevance of these somatosensory parcellation results indicates the feasibility of a wide range of potential applications to brain mapping.

Introduction

Classical approaches for parcellating the cerebral cortex are based on histological features (Brodmann, 1909; Vogt & Vogt, 1919; Economo, 1926; Sanides, 1970; Triarhou, 2007). The high interindividual variability of the anatomical/functional areas and the difficulty of using non-invasive imaging techniques to identify histological features of brain tissue are the main motivations for developing novel parcellation approaches (Amunts *et al.*, 1999; Geyer *et al.*, 2011; Van Essen & Glasser, 2013). With non-invasive functional magnetic resonance imaging (fMRI), the cerebral cortex can be parcellated into different functional units via motivated tasks (Heeger & Ress, 2002). Recently, several groups have developed task-free methods based on measures of structural and functional connectivity for the parcellation of the human cerebral cortex, e.g. Broca area (Anwander *et al.*, 2007; Kelly *et al.*, 2010), lateral premotor cortex (Schubotz *et al.*, 2010), temporal pole (Fan *et al.*, 2013), thalamus (Serra *et al.*, 2013), cingulate cortex (Beckmann *et al.*, 2009; Yu *et al.*, 2011), primary motor (MI) area (Gorbach *et al.*, 2011; Nebel *et al.*, 2012), medial frontal cortex (Johansen-Berg *et al.*, 2004), frontal pole (Liu *et al.*, 2013), lateral frontal cortex (Goulas *et al.*, 2012),

inferior parietal cortex (Ruschel *et al.*, 2013), precuneal cortex (Margulies *et al.*, 2009; Zhang & Li, 2012), lateral parietal cortex (Nelson *et al.*, 2010), anterior cingulate cortex (Margulies *et al.*, 2007) supplementary motor area (Kim *et al.*, 2010) and primary somatosensory (SI) cortex (Roca *et al.*, 2010), etc. The advantage of these methods is that no modality-specific tasks are necessary to identify functional subregions, making it an ideal approach for characterising brain organisation in clinical and longitudinal studies (Knosche & Tittgemeyer, 2011; de Reus & van den Heuvel, 2013; Wig *et al.*, 2013b).

We aimed to parcellate the human sensorimotor cortex, consisting of the contiguous MI and SI areas, into functionally meaningful subunits using resting-state fMRI (rs-fMRI) data. Based on their cytoarchitecture, the MI includes Brodmann area (BA) 4 (Campbell, 1905), and the SI includes BA 3, BA 1 and BA 2 (Brodmann, 1909; Vogt & Vogt, 1919; Geyer *et al.*, 1999, 2000). The sensorimotor cortex presented somatotopic organisation, with subregions relating to different body parts (Penfield & Boldrey, 1937; Kaas *et al.*, 1979; Okada *et al.*, 1984). This organisation within the SI/MI was also found via multiple motor/tactile tasks (Rao *et al.*, 1995; Stippich *et al.*, 1999; Lotze *et al.*, 2000; Meier *et al.*, 2008; Buckner *et al.*, 2011).

Recently, the subregions within the sensorimotor cortex were found to be organised ventral-to-lateral using rs-fMRI or diffusion-weighted imaging (van den Heuvel & Hulshoff Pol, 2010; Roca

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et al., 2010; Cauda et al., 2011; Yeo et al., 2011; Jo et al., 2012; Nebel et al., 2012). Whether the extent of parcellations based on rs-fMRI data spatially corresponds to these somatotopic subdivisions remains to be quantitatively assessed. In the present study, we assessed whether the parcellation of the primary sensorimotor cortex using rs-fMRI corresponds to the representations of upper–middle–lower limb segmentation.

Materials and methods

Data

Two datasets were included in the present study (Dataset I and II). Each dataset was composed of rs-fMRI and motor task fMRI data for the aim of comparing the results of functional connectivity-based parcellation with the task-induced activation related to the movement of body parts. Dataset I included one resting-state session that was scanned after a task session in order to investigate the post-task effect on the parcellation analysis.

Dataset I: Max Planck Institute

Participants

Nine right-handed adult participants were enrolled in the present study at the Max Planck Institute (MPI) for Human Cognitive and Brain Sciences in Leipzig (two females; age 27 ± 2.12 years). All participants were enrolled from the local university and had no history of any psychiatric or neurological disease. The present study was approved by the local ethics committee and written informed consent was given by each participant. The Code of Ethics of the World Medical Association (Declaration of Helsinki), printed in the British Medical Journal (18 July 1964), was followed by the present study.

Magnetic resonance imaging data acquisition

All data were acquired using a 3-Tesla magnetic resonance imaging system (Verio, Siemens, Erlangen, Germany) equipped with a 32-channel head-coil. The common parameters for all fMRI sessions were as follows: gradient-echo echo-planar imaging sequence, interleaved slice-timing, gap, 1 mm; repetition time (TR), 2 s; echo time (TE), 30 ms; flip angle, 90º; matrix size, 64×64. For each participant, five fMRI sessions were acquired with a break of 10 s in between (Fig. 1C). The first two sessions and the fourth session were

resting-state sessions of 6 min each. The third and fifth sessions were motor-task sessions of 12 min each. For the resting-state sessions, 30 axially-oriented slices over the whole brain were collected with a voxel size of $3 \times 3 \times 4.8$ mm. For the task sessions, 20 coronally-oriented slices with a voxel size of $2 \times 2 \times 2.2$ mm were obtained surrounding the central sulcus (Fig. 1A). The parameters for the magnetization-prepared rapid gradient-echo (MPRAGE) T1-weighted image sequence were: 12-channel coil, flip angle, 9°; 176 slices; TR, 2300 ms; TE, 2.96 ms; voxel size, $1 \times 1 \times 1$ mm; matrix size, 240×256; inversion time, 900 ms. Visual projection was by a mirror fixed to the head-coil and a projector located outside the scanner room.

Participants lay supine in the scanner with their head fixed using foam pads to minimise head motion. During the three resting-state sessions (i.e. Rest1, Rest2 and Rest3), participants were instructed to focus on a white fixation cross with a black background, and to remain motionless and not think of anything in particular. Rest3 was scanned after the first task session for the post-task effect investigation.

During the task session (i.e. Task1 and Task2), participants were asked to perform a movement task (Fig. 1B). Each block included 25 s of active movement and 15 s of rest. There were three types of movements in this task: 'tapping right fingers', 'moving tongue within the mouth', and 'moving right foot and toes'. All movements were performed at a self-defined pace throughout the active block. The German word for the respective body part ('Hand', 'Fuß' or 'Zunge') was displayed in place of the cross to indicate which body part to move. The word was projected in white with a black background in the center of the mirror. For each body part, six blocks were counterbalanced.

Dataset II: Human Connectome Project

A second dataset was provided by the Human Connectome Project (HCP), supported by the WU–Minn Consortium and McDonnell Center for Systems Neuroscience at Washington University (Van Essen et al., 2013). The dataset consisted of 68 left-handed and right-handed healthy participants (50 females) in the HCP quarter 1 (released online: March 2013). Thirty-six participants (18 females, age 26–35 years) were selected for the present study, with specific attention paid to matching male and female participants.

For each participant, one rs-fMRI session (with left-to-right direction phase encoding) and the motor task fMRI session were analysed. The scan parameters of the rs-fMRI data were: TR, 720 ms; TE, 33.1 ms; flip angle, 52°; field of view,
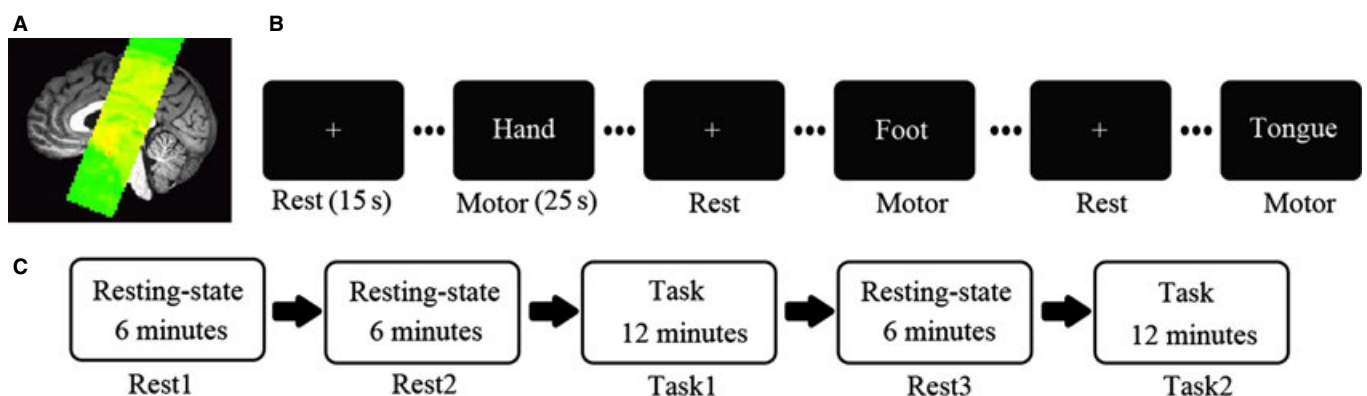
FIG. 1. Both resting-state and task-based data were included in the present study. (A) The green area represents the slices obtained during the task session for each participant. (B) A block-design paradigm was used in the task session. Visual stimuli instructed participants to move the respective body parts. (C) The experiment consisted of five sessions including resting periods and tasks, and lasted for approximately 1 h. The gap between sessions was around 20 s.

208 × 180 mm; slice thickness, 2.0 mm; 72 slices; voxels isotropic, 2.0 mm; multiband factor, 8; echo spacing, 0.58 ms; Bandwidth (BW), 2290 Hz/Px; time points, 1200 (Feinberg *et al.*, 2010; Moeller *et al.*, 2010; Setsompop *et al.*, 2012; Xu *et al.*, 2012). The task paradigm was similar to that used in the acquisition of the MPI dataset. Participants were asked to move their right or left hand, toes and tongue with 12-s blocks and a 3-s cue. A total of 284 time points were obtained during the motor task session.

Analysis

Dataset I: Max Planck Institute

All images were preprocessed as follows using SPM5 (www.fil.ion.ucl.ac.uk/spm/): slice-timing correction, motion correction, spatial normalisation to the Montreal Neurological Institute 152 space, sampled to 3 × 3×3 mm voxel size, and spatial smoothing with 6-mm full-width at half-maximum of the Gaussian kernel. All participants had < 1 voxel translation (3 mm) or 1° rotation head motion. For the resting-state data, the REST toolbox (www.restfmri.net/) was used with the following parameters: (i) band-pass filtering (0.01–0.08 Hz); (ii) removing the linear trend of time courses; and (iii) regressing out six head motion parameters, average time courses from a white matter mask and a cerebral spinal fluid mask (Fig. 2).

Task-based analysis

The activation maps of each body part were generated using a general linear model analysis in SPM5. A one-sample *t*-test was performed on the beta intensity maps across participants for each body part. All t-maps were thresholded at $p < 0.05$ using AlphaSim in AFNI (Cox, 1996).

Connectivity-based parcellation analysis

The connectivity-based parcellation analysis was the same for all three resting-state sessions (see Fig. 2).

1 Considering the anatomical variations across participants and the spatial resolution of fMRI data, we selected an area including both the MI and SI along the central sulcus. A template mask including the left BA 4 and BA 3 from the Anatomy toolbox was selected as the region of interest (ROI; Fig. 2-1; Geyer *et al.*, 1999, 2000; Eickhoff *et al.*, 2005).

2 Spatial correlation maps between each voxel within the ROI were calculated and transformed using Fisher's r-to-z (Vincent *et al.*, 2007; Yeo *et al.*, 2011; Fig. 2-2).

3 An eta^2 value was then calculated for each pair of voxels' z-transformed connectivity maps, generating a similarity matrix (Fig. 2–3) for each individual (Cohen *et al.*, 2008). Group-level analysis was conducted on data averaged across each resting-state session from each participant separately.

4 Finally, both the individual similarity matrix and group-averaged matrix were classified into between two and 10 clusters by spectral K-means using the multicut clustering algorithm (Fig. 2-4/5; with 1000 iterations using the Spectral Clustering Toolbox; Meila & Shi, 2001; Kelly *et al.*, 2010).

5 The optimal number of clusters was investigated using two approaches at the group level. The Dice coefficient (DC; from 0 to 1, where 1 is the highest overlap) was calculated for each *k*'s
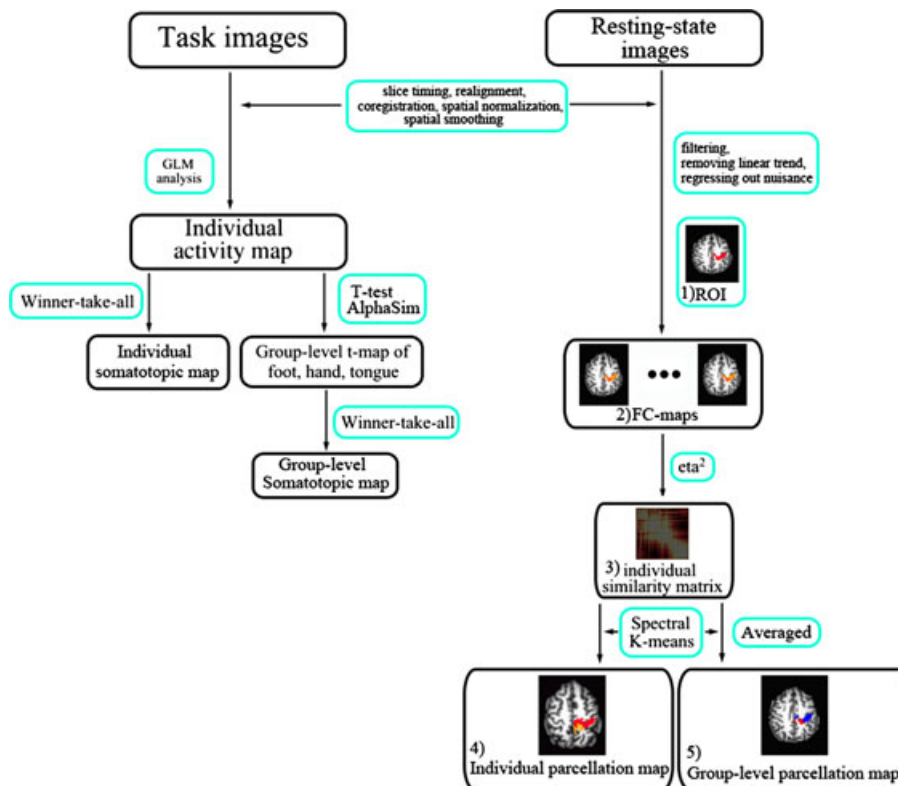

FIG. 2. The processing steps for task and resting-state data. 5 steps are displayed for the parcellation analysis: 1) The ROI selection; 2) The functional connectivity analysis; 3) Generating the similarity matrix; 4) and 5) Generating the parcellation maps. The black frame indicates the results, and the blue frame indicates the processing methods. The task images provided activation areas for foot, hand and tongue. From the resting-state images, clusters were generated based on the correlation maps of voxels within the ROI. The results of the task and resting-state sessions were further analysed for similarity using the DC. FC, functional connectivity; GLM, general linear model.

solution between the first and second resting-state sessions to test the stability of each k (Dice, 1945; Nebel *et al.*, 2012). In addition to the DC calculation, the silhouette was also calculated for the three MPI resting-state sessions (Kelly *et al.*, 2010). The silhouette value is a ratio between the similarity of a voxel to others within the same cluster and to those outside it. A higher silhouette indicated higher reliability of the clusters.

Assessment of correspondence between task and resting state

Three assessments evaluated the spatial correspondence between task-derived regions and the resting-state clusters.

Group-level analysis

A winner-take-all (WTA) analysis was performed on the group-level t-maps of two task sessions derived from the foot, hand and tongue within the left BA 3 and BA 4 ROI (Meier *et al.*, 2008). A voxel was assigned as one limb area if the *t*-value of one body part was higher than the others. The overlap ratio was then calculated between the WTA map and the three-cluster parcellation map from three resting-state sessions. The DC was also calculated between WTA maps of the two task sessions. Here the overlap ratio between two maps that both had three clusters was not calculated cluster by cluster as the normal DC. As both maps had the same number of clusters and the same ROI size, the overlap ratio was calculated by summing the number of overlap voxels for each pair of clusters, and then dividing it by the number of voxels within the whole ROI.

Individual-level analysis

WTA analysis was performed on each individual's Task1 t-maps of the foot, hand and tongue within the ROI. For each k solution, the DC was calculated between the area of the WTA map and the clusters from the Rest1 parcellation map. The three highest cluster pairs were averaged. The parcellation map with the highest average DC is presented (Fig. 5). In addition, the averaged maximum DC value between the Task1 WTA maps and the parcellation map of the Rest2 and Rest3 was also calculated for each participant.

Within each cluster of the resting-state parcellation map ($k = 3$ for each session), the averaged and SD values of Task1's group-level t-maps (foot, hand and tongue) were calculated.

Assessing relationships between body parts

For the MPI data, a 6-mm radius sphere was created for the representations of each body part centered on the group-level peak voxel from each (foot: $[-3, -24, 75]$; hand: $[-39, -21, 60]$; tongue: $[-54, -9, 33]$, MNI standard space). For each participant, the average time series within each sphere were correlated from the three resting-state sessions.

Three clusters, which were selected from the parcellation maps of each resting-state session, were used as the upper, middle and lower limb regions. The correlation coefficients between these clusters were then calculated (in Fig. 3B: red cluster, lower limb region; green cluster, middle limb region; yellow cluster, upper limb region). For both correlation coefficients (one obtained from Task1 and the other from resting-state clusters), a paired *t*-test between middle–lower (i.e. hand–foot), lower–upper (i.e. foot–tongue) and middle–upper (i.e. hand–tongue) was performed across participants.

Dataset II: Human Connectome Project

All fMRI data were first preprocessed in the HCP pipeline using FSL (FMRIB Software Library, Woolrich *et al.*, 2001; Jenkinson *et al.*, 2002, 2012; Fischl, 2012; Glasser *et al.*, 2013). For the resting-state data, the REST toolbox was used as described for the MPI dataset: band-pass filtering, removing linear trend of time courses, regressing out six head motion parameters, average time courses from a white matter mask and cerebral spinal fluid mask. For the task data, only the activation of the right hand, right foot and tongue were selected. The WTA map was created based on the t-map of these three body parts.

The parcellation analysis for the HCP quarter 1 data was performed in the same way as for the MPI data. The BA 3/4 ROI was used. The similarity matrix for each participant was generated via the connectivity-based analysis. Three clusters were detected on the group-level averaged similarity matrix using the spectral K-means approach. The DC between the WTA map and group-level parcellation map was calculated.

Results

Activation areas for body parts

The general linear model analysis of the task sessions revealed activation areas for the hand, foot and tongue for both task sessions. Here we only focus on activations within the SI and MI. Owing to the sensory aspect implicit in any motor task, the SI and MI were both activated. The foot region was detected in the left paracentral lobule, the hand region in the left pre/postcentral gyrus, and the tongue region in the bilateral inferior post/precentral gyrus (Fig. 3A). The activation areas for all body parts were consistent across both task sessions. In addition, the upper–middle–lower limb segmentation was represented in the WTA map (Fig. 3B). The DC between two WTA maps of two task sessions was 0.9516.

Clustering of resting-state data

Three subregions were found on the group-level connectivity-based parcellation analysis using the resting-state data (Fig. 3B, second row). Consistent with hypotheses of somatotopic organisation, the superior-most region was located ventromedially, a second region was located dorsolaterally and a third region was located inferiolaterally. This spatial distribution was similar across three resting-state sessions. This somatotopic organisation was also found in the parcellation maps with different cluster numbers (Fig. 3C).

The Dice coefficients (DCs) between the parcellation maps of the two resting-state sessions indicated that high stability was found when k was 3 (Fig. 4A). Across the three resting-state sessions, the silhouette value was the highest when k was 2, and the second highest value in k was 3. All silhouette values did not change dramatically across all k solutions (Fig. 4B).

Correspondence between task regions and resting-state subregions

At the group-level, resting-state subregions corresponded to the subregions observed in the task-based WTA map. All three parcellation maps demonstrated a high DC (> 0.75) with the task's WTA map (Fig. 3B). Individual DCs between the parcellation map from the Rest1 and the WTA map from Task1 are shown in Fig. 5A. All
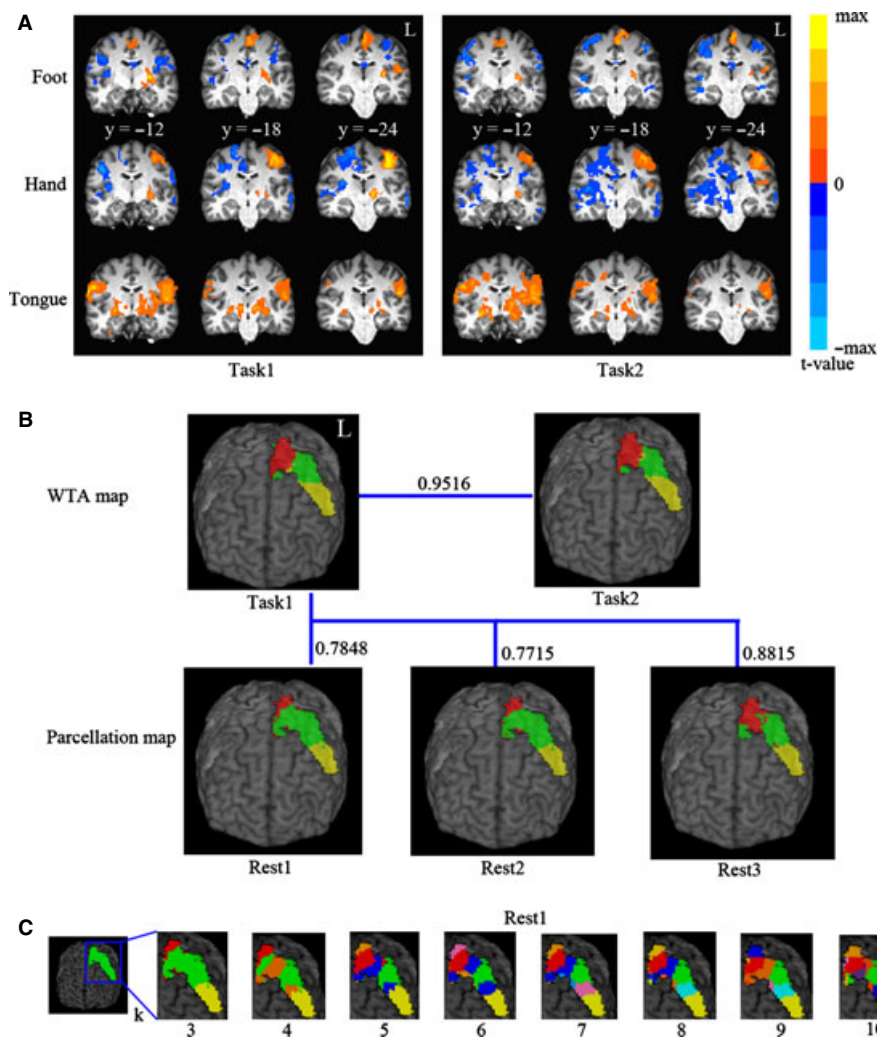
FIG. 3. (A) Each row represents the result from one body part. The group-level activity regions of right foot, right hand and tongue were found in both task sessions. All t-maps were corrected at $P < 0.05$ and merged on one participant's structural T1 image. Warm color represents positive value and cold color represents negative value. The coordinates are in Montreal Neurological Institute space. L, left hemisphere. (B) The upper row shows the group-level WTA map across three t-maps of right foot, right hand and tongue from the two task sessions. Yellow color represents upper limb, green color represents middle limb and red color represents lower limb. The lower row presents the map from the group-level functional connectivity-based parcellation analysis of three resting-state sessions. Number of clusters (k) was set to three. The colors corresponding to three clusters are yellow, green and red. The DC between each pair of maps is presented near the blue lines. (C) The parcellation maps from Rest1 with different numbers of clusters are presented. Different colors indicate different clusters.

participants' maximum overlap DC ratios were greater than 0.55. The highest DC in several individuals was observed for $k > 3$ due to the detection of small clusters (e.g. s04 and s07) in the parcellation analysis.

The averaged and SD values of three t-maps of Task1 within each cluster are presented in Fig. 6. Each cluster from resting-state data had the highest value to the t-map from only one body part. Their spatial distribution was also somatotopically organised.

Post-task effect on the parcellation analysis

At the group level, the parcellation map of Rest3 presented the highest DC with Task1's WTA map (Fig. 3B). At the individual level, an increased trend of DC was observed from Rest1/Rest2 to Rest3 (Fig. 5B). Rest3 presented a significantly higher DC than Rest2 and Rest1 ($P < 0.05$) across participants. No significant difference was found between Rest1 and Rest2 (Fig. 5B).

Relationships between three body parts

The hand–foot, hand–tongue and foot–tongue correlation, using the task-peak sphere and the clusters from the parcellation analysis, were also examined across three resting-state sessions (Table 1, left). Both the hand–foot and hand–tongue correlation were significantly higher than the foot–tongue correlation across participants and the first two resting-state sessions. Moreover, there was no significant difference between the hand–foot and hand–tongue correlation (Table 1, right).

Results from the Human Connectome Project data

The activity areas of the right foot, right hand and tongue were similar to those found in the MPI dataset (Fig. 7A), and the somatotopic organisation was also observed. High correspondence between the task WTA map and resting-state parcellation map was detected (Fig. 7B; DC = 0.8441).
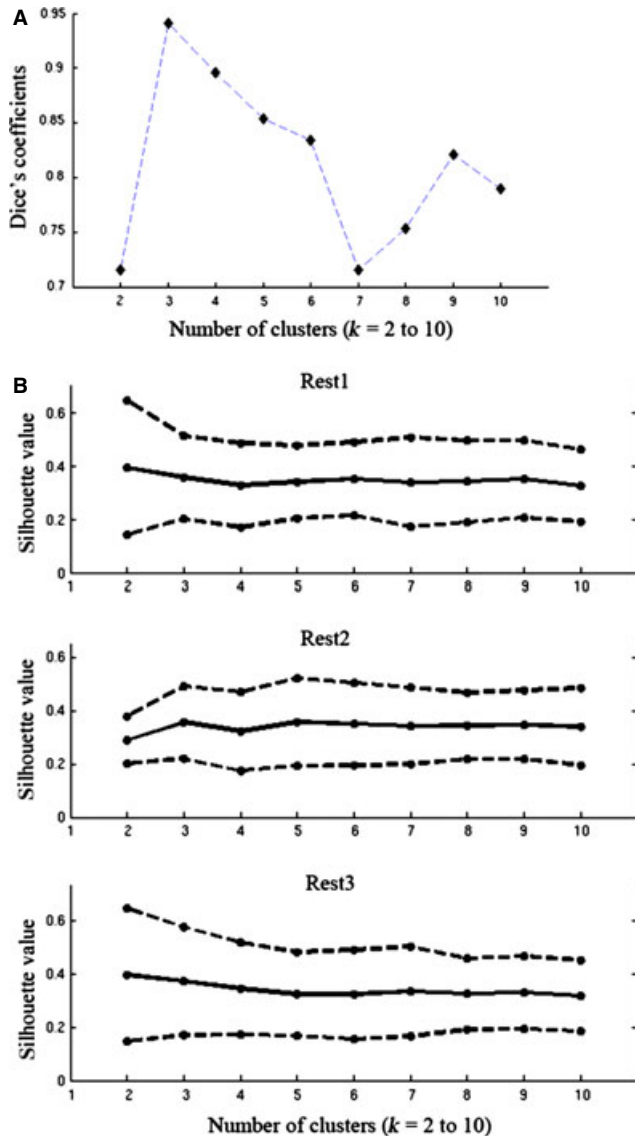
FIG. 4. (A) The DC value between the parcellation maps of Rest1 and Rest2 across different *k*. Each diamond shape represents one selection of *k* for the DC calculation between two close resting-state sessions' parcellation maps. (B) The silhouette value of the detected clusters across three resting-state sessions. The mean and SD value are presented. The solid line indicates the mean value, and the dashed line indicates the SD.

Discussion

We observed that rs-fMRI-based parcellation of the sensorimotor cortex, corresponding to BA 3 and BA 4, identifies somatotopically arranged clusters in two independent datasets. These clusters correspond spatially to a somatotopic representation of upper–middle–lower limb segmentation, as identified by task-based fMRI. Interestingly, the resting-state parcellation map demonstrated higher correspondence to the task-based divisions after individuals performed a motor task.

Somatotopic organisation revealed by resting-state functional magnetic resonance imaging

We found somatotopic organisation within the left sensorimotor cortex. Precentral and postcentral gyrus (motor and somatosensory

regions were subdivided into three clusters, depending on the individual dataset, from dorsomedial to ventrolateral along the central gyrus (Fig. 3). Considering the spatial resolution of fMRI and the variation of anatomical structure near the central sulcus across participants, we applied the connectivity-based parcellation analysis on the conjunction of the MI and SI. Before the present study, several previous studies had also found similar distribution of clusters within the MI and SI by connectivity-based parcellation analysis (Roca *et al.*, 2010; Schubotz *et al.*, 2010; Gorbach *et al.*, 2011; Nebel *et al.*, 2012). Although the number of clusters was variable, dorsomedial–ventrolateral organisation was a common feature across these studies. The whole-brain voxel-wise connectivity-based parcellation analysis also detected two parts of the somatomotor area, dividing it into a lower face and upper hand–foot region during rest (Yeo *et al.*, 2011). Our study confirmed that this somatotopic organisation could be found using rs-fMRI data, and this organisation was reliable across different resting-state sessions and datasets. Importantly, we validated the somatotopic arrangement by showing the correlation between subregions identified by resting-state-based parcellation and representations of body parts as identified by task-based fMRI. Different body sectors seem to have characteristic functional connectivity features along the central gyrus that have separable domains (van den Heuvel & Hulshoff Pol, 2010).

Resting-state clusters and activations related to different body parts

We compared resting-state clusters and activation areas from the task (Figs 3 and 6). For both datasets, firstly, three clusters were found in the group-level analysis. These clusters were equally distributed and displayed high correspondence with the WTA map derived from the tasks (Figs 3 and 6). A high overlap (DC > 0.75 for the MPI dataset; DC = 0.8441 for the HCP quarter 1 dataset) confirmed three distinguishable areas using two different fMRI modalities. Similar results were also found at the individual level (Fig. 4A). The averaged value within each resting-state cluster showed a good one-to-one correlation with the respective cerebral representations of the different body parts (Fig. 5). Previous studies had reported that the motor cortex consists of three separate sectors: lower body, middle section and head (Meier *et al.*, 2008; Yeo *et al.*, 2011; Weiss *et al.*, 2012). According to our approach, these three sectors could be distinguished from the others based only on the resting-state functional connectivity patterns within the sensorimotor cortex.

The post-task effect to the parcellation analysis

The Rest3 session was scanned after the Task1 session. Interestingly, the parcellation maps of Rest3 showed higher correspondence with the Task1 WTA map than the other two resting-state sessions at both the group- and individual-level. It was reported that the resting-state needs a period of time to return to a task-free baseline state after the performance of tasks (Barnes *et al.*, 2009), and motor learning can affect subsequent activity within resting-state networks (Albert *et al.*, 2009). The repetitive movements of alternate body parts could be considered as a simple training task, and this task affected the sensorimotor cortex functional organisation in the following resting state as the gap between Task1 and Rest3 was short (around 20 s). The subdivisions of the sensorimotor cortex might consolidate and vary through motor-training tasks (Taubert *et al.*, 2011; Tung *et al.*, 2013). It was also possible that participants
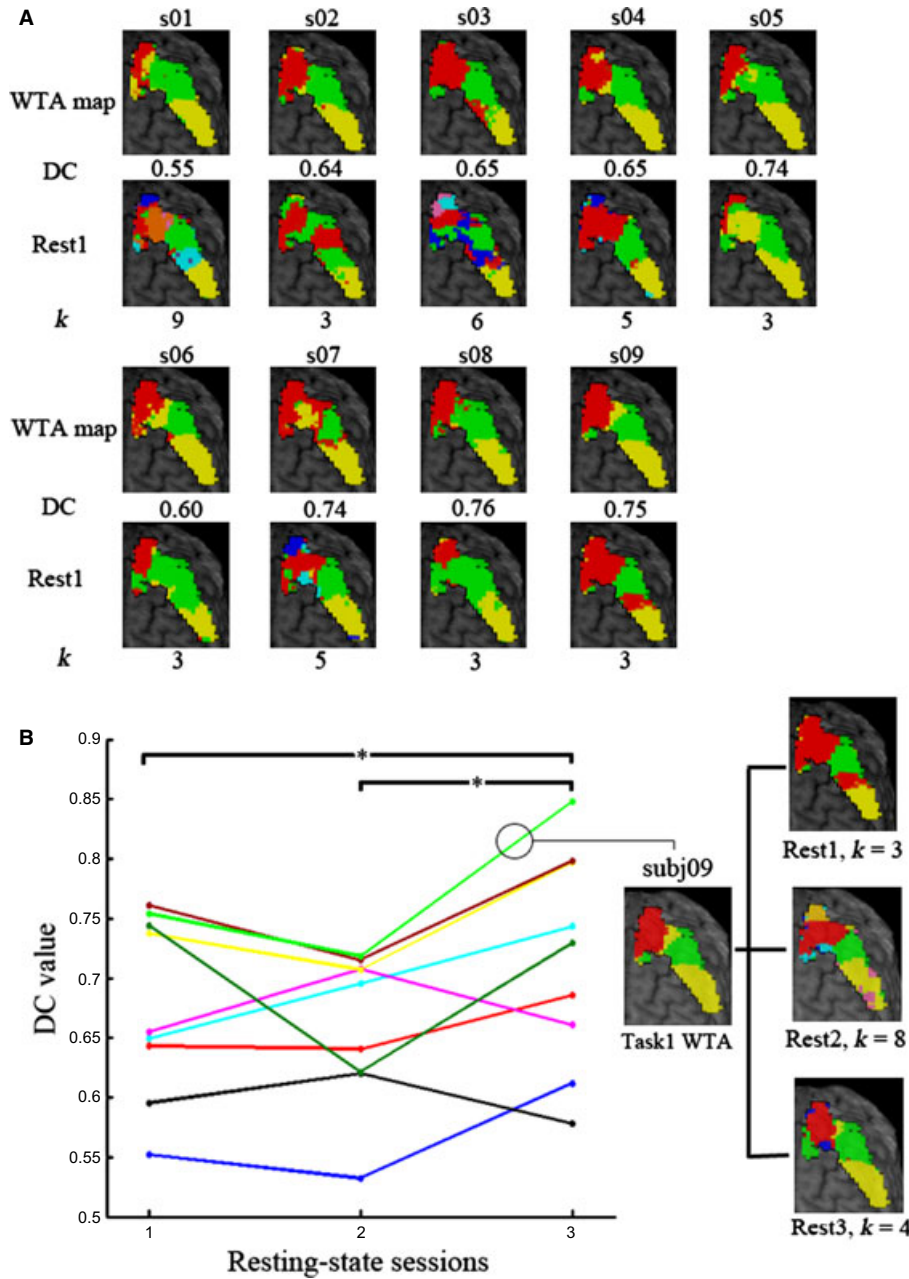
FIG. 5. (A) The parcellation map that gives the highest averaged DC and the WTA map for each participant are displayed. The DC is presented between these two maps. The *k*-solution that had the maximum averaged DC for each participant is indicated below. (B) The averaged maximum DC values between the Task1 WTA maps and resting-state parcellation maps are presented for each participant across three resting-state sessions. One color indicates one participant. The dots represent the averaged maximum DC value for each resting-state session. *Significant difference between sessions ($P < 0.05$). One participant's WTA map of Task1 and parcellation maps of three resting-state sessions are displayed (i.e. green line in B).

imagined the previous motor tasks during the resting session, thereby activating it (Stippich *et al.*, 2002). Duff *et al.* (2008) found that the task-activated regions presented increased signal spectral power in the post-task session. To our knowledge, this is the first time that this plasticity effect was detected in the resting-state functional connectivity-based parcellation analysis. We suggested that the functional subregions that were detected during the resting state should take task effects into account. This effect could also lead the morphometry difference between task-based regions and resting-state regions.

Robust activations corresponding to body parts by movement task

For the MPI dataset, each participant performed three different movements engaging the foot, hand, and tongue. The motoric activity was inherently accompanied by sensory stimulation. We asked participants to perform these tasks in two separate sessions, in order to identify whether the activations were robust and consistent. Several studies had previously reported somatotopically arranged functional regions corresponding to the hand, foot and tongue within the
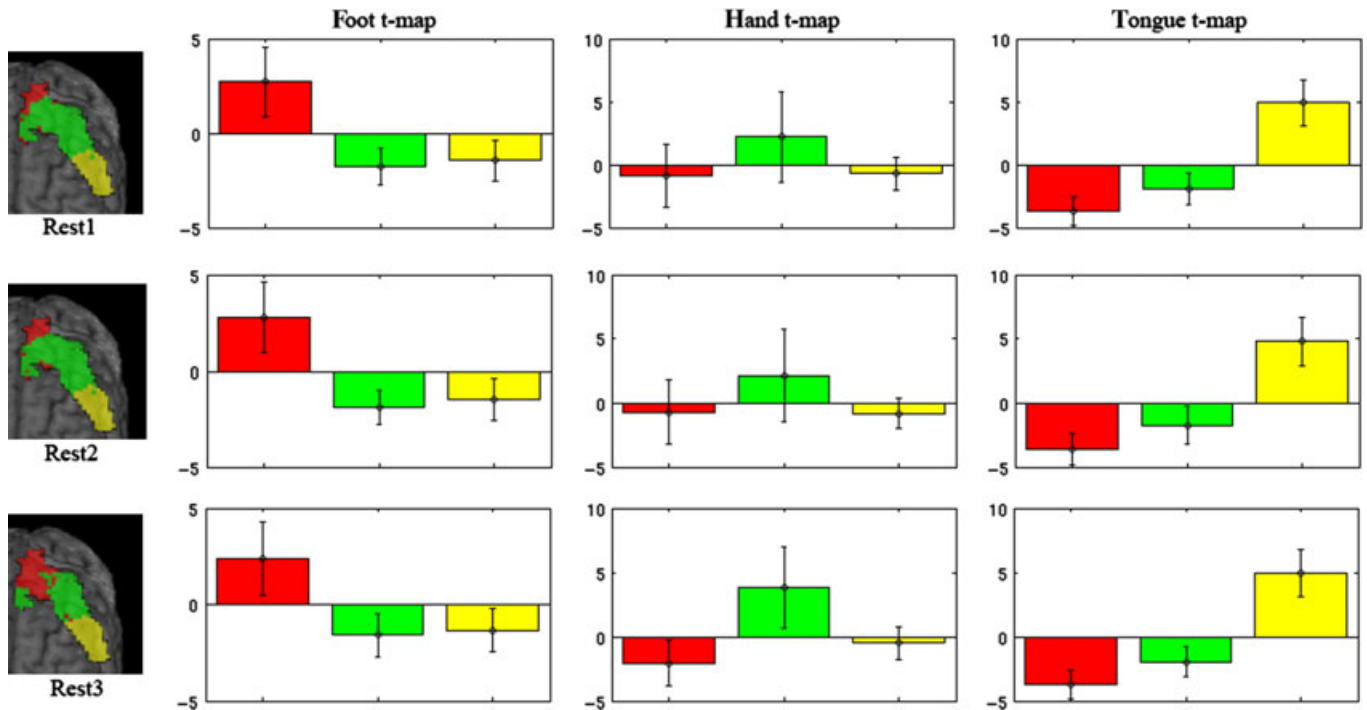
FIG. 6. For each row, the three-cluster parcellation map from the resting-state session was merged on one participant's T1 image. Each color represents one cluster. The averaged and confidence intervals of *t*-values from the Task1 t-map of the right foot, right hand and tongue within each cluster are given, respectively. The color of each bar picture was assigned according to each cluster.

TABLE 1. Correlation analysis of body part ROIs

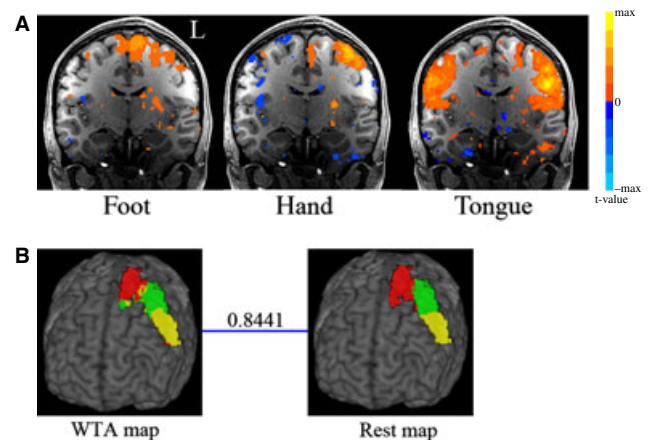| Session	*r* (rest)	*r* (task)		Rest ROI	Task ROI
Rest1					
Hand–foot	0.8986	0.5321	H–F > F–T	0.0001	0.0227
Hand–tongue	0.8316	0.5096	H–T > F–T	0.0062	0.0324
Foot–tongue	0.5317	0.2292	H–F > H–T	0.5890	0.8538
Rest2					
Hand–foot	0.8016	0.5700	H–F > F–T	0.0005	0.0114
Hand–tongue	0.9493	0.6744	H–T > F–T	0.0078	0.0027
Foot–tongue	0.5427	0.3365	H–F > H–T	0.3088	0.3481
Rest3					
Hand–foot	0.9820	0.4544	H–F > F–T	0.0004	0.0096
Hand–tongue	0.7794	0.6503	H–T > F–T	0.1347	0.0110
Foot–tongue	0.6434	0.2221	H–F > H–T	0.0209	0.1559

H, hand; F, foot; T, tongue.

FIG. 7. (A) The group-level activity maps of the right foot, right hand and tongue are displayed. Coordinate Y is 12 mm in Montreal Neurological Institute space. Warm color represents activation and cold color represents deactivation. L, left. (B) The WTA map and parcellation map are presented. The DC between these two maps is above the blue line. For the WTA map, the upper, middle and lower limb area was indicated in yellow, green and red. The red, green and yellow color in the parcellation map indicates clusters.

MI and SI using task-based fMRI (Meier *et al.*, 2008; Buckner *et al.*, 2011; Weiss *et al.*, 2012), and the results have been shown to be highly reproducible across different sessions (Weiss *et al.*, 2012). Our results showed similar stability of upper–middle–lower limb segmentations across the two task sessions (Fig. 3). These patterns were also found in the HCP quarter 1 dataset (Fig. 7A). These results provide initial validation for describing the somatotopic arrangement of subareas derived exclusively from rs-fMRI data.

Relationships between representations of body parts

The rs-fMRI data also allowed us to investigate the correlations between the different somatotopically arranged clusters. The ipsilateral right foot–hand and hand–tongue show similar correlation values, which were both higher than the foot–tongue relationship. The foot–tongue presented no significant correlation. This result was

similar to the findings of Yeo *et al.* (2011). They found a higher correlation between the right foot–hand than between hand–tongue, and the lowest correlation between foot–tongue. Unlike the current findings, Yeo *et al.* (2011) found the foot–tongue to have a significant correlation. Although these different results may be explained by the substantially larger sample size (n = 1000) in the study of Yeo *et al.* (2011), the ranking of the three pairs was nonetheless consistent.

Although the spatial proximity of hand, foot, and tongue representation in the brain may contribute to the current findings, the

correlation of the blood oxygenation level dependent (BOLD) signal between body parts may also be explained by basic motor habits. The hands and feet present high interlimb coordination (Swinnen & Carson, 2002), and hand and tongue coordination is frequently necessary, e.g. during talking and eating (Gentilucci & Campione, 2011). In contrast, the foot and tongue are rarely behaviorally coupled. Spontaneous movements (or movement inhibition) in the magnetic resonance imaging scanner could also contribute to our findings.

Limitations

Although a 'standard' spatial resolution of 3 mm^3 was used in the present study, it might not be precise enough to differentiate small anatomical units in sensorimotor areas. In our parcellation analysis, boundaries were only detected between upper, middle and lower limb, which was confirmed by the dominant activation area of foot, hand and tongue. These three sections might also be activated by movement of other body parts, e.g. arm and lips, which was beyond the scope of the current study. The segments also have smaller units such as toes and fingers, which could be detected by fMRI (Blankenburg *et al.*, 2003; Sanchez-Panchuelo *et al.*, 2012). In future studies, a higher spatial resolution could allow for a higher number of parcellations targeting smaller functional units. Also, the peak activity area for a specific body part, such as the tip of the index finger, could help in investigating resting-state subregions, rather than boundary detection from WTA analysis of task images (Meier *et al.*, 2008).

The estimation of the optimal number of clusters in the sensorimotor cortex required *a priori* knowledge and remains a methodological challenge. To date, several studies have taken the measure of cluster stability across bilateral areas (Kahnt *et al.*, 2012), sessions (Nebel *et al.*, 2012) and individuals (Schubotz *et al.*, 2010; Liu *et al.*, 2013) to select the optimal number of clusters. Cluster parameters such as silhouette have also been employed for cluster number validation (Kelly *et al.*, 2010). In the present study, the three body parts investigated limited the desired cluster number. Despite a range of cluster numbers investigated, we focused here on the three-cluster solution to match the number of activated areas.

The method that we performed was based on functional connectivity features from the BOLD signal correlation. The results represent somatotopic separation rather than the separation of cytoarchitectonically defined areas, i.e. BA 3a, BA 3b and BA 4 (Geyer *et al.*, 1999, 2000; Wig *et al.*, 2013a). Ongoing lines of research to identify BA regions in the SI through *in vivo* imaging (Geyer *et al.*, 2011) and functional connectivity analysis in the SI with ultra-high field imaging in monkey (Wang *et al.*, 2013) may also provide helpful tools for the validation of rs- fMRI-based parcellation approaches in the future.

Conclusions

We were able to identify segregated functional regions within the left MI/SI using rs-fMRI and validate its somatotopic arrangement through comparison to task-based activations with two independent datasets. The posteffect of the motor task on the resting-state parcellation map was observed. This methodology may also be applicable to clinical investigation requiring the identification of different body parts. The question remains regarding the level of detail that rs-fMRI may be able to provide for characterising functional regions. Improvements in spatial resolution will enable the investigation of unique dynamics between the MI and SI, as well as potentially further subdivisions consistent with cytoarchitectonic areas.

Acknowledgements

Abbreviations

BA, Brodmann area; DC, Dice coefficient; fMRI, functional magnetic resonance imaging; HCP, Human Connectome Project; MI, primary motor; MPI, Max Planck Institute; ROI, region of interest; rs-fMRI, resting-state functional magnetic resonance imaging; SI, primary somatosensory; WTA, winner-take-all.

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Chapter 3: Outlook

The present thesis outlines a non-invasive, *in vivo* method to delineate subregions within the sensorimotor cortex. By validating this data with task-based motor activation of these regions, results indicate that functional subregions of the hand, foot and tongue within the sensorimotor cortex are in fact revealed by resting-state fMRI data. Because of the reliability and ease with which this data can be acquired, the present thesis points towards a reliable method which would be applicable for both individual, clinical settings, as well as the analysis of large scale data sets. These possibilities are presented in more detail below.

As previous studies have shown, each part of the human body is related to different sensorimotor areas (Penfield & Boldrey, 1937; Kaas *et al.*, 1979; Okada *et al.*, 1984). For instance, a set of brain areas which were active during the electrical stimulation from fingertip to palm of hand (Fig. 1) was somatotopically organized from rostral to caudal in SI (Blankenburg *et al.*, 2003). Since the region for hand was detected in the present analysis, it may be possible to detect regions with even finer spatial resolution (e.g., fingers) via connectivity-based parcellation analysis (Sanchez-Panchuelo *et al.*, 2012). Future work will be dedicated to building a more comprehensive map of the human body.
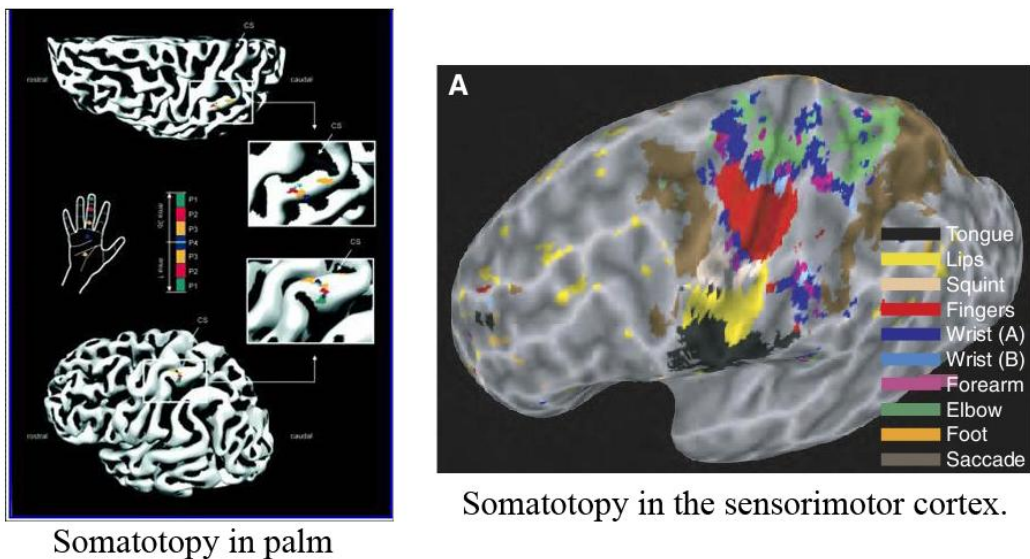
Somatotopy in palm

Somatotopy in the sensorimotor cortex.

Figure 1. Previous studies have detected sets of body parts in the sensorimotor cortex using task-based fMRI. The image on the left presents several activation regions corresponding to areas from the tip of the finger to the palm arranged orderly within a Brodmann area and mirrored onto the adjacent Brodmann area (adapted from Blankenburg et al., 2003). The image on the right shows activation areas of different body parts. The image is adapted from Meier and colleagues' study (Meier *et al.*, 2008).

A somatotopic atlas of the human body could provide complimentary information about human brain function alongside other anatomy-based templates (Rorden & Brett, 2000; Tzourio-Mazoyer *et al.*, 2002) as well as the possibility for creating population-level ROIs for researchers. Similarly, studies interested in the plasticity of somatotopic arrangement of body parts in the cortex, or their development, could be performed easily and conveniently.

While there is a remarkable differentiation between bodily regions in the present study, distinctions between sensory and motor regions--which could be expected based on the cytoarchetectonics--are not observed. In previous studies this subdivision between motor and somatosensory cortex was also difficult to detect through rs-fMRI (Long *et al.*, 2014; Nebel *et al.*, 2014), as well as DWI (Roca *et al.*, 2010). To date, boundaries between BAs within the sensorimotor cortex have only

been detected in vivo by ultra-high-field MRI scanner, through variations of myelination or cortical thickness changes (Geyer *et al.*, 2011; Sanchez-Panchuelo *et al.*, 2014).

Future research might combine different approaches for parcellation. For example, in a first step BA 4 and BA 3 might be parcellated based on structural MRI and in a second step somatotopy within BA 4 and BA 3, respectively, might be identified using resting state fMRI. Such experiments will almost certainly need to be carried out at a higher magnetic field than the present study, i.e., 7 Tesla. Pre-processing methods may also play a role in the perceived functional overlap between these regions.

There may also be clinical applications for resting-state connectivity-based analysis of fMRI data. To mention just one example: Children with autism in one study (Nebel *et al.*, 2014) were shown to have an atypical somatotopic organization. In the future, similar rs-fMRI analysis may be employed in order to investigate organization changes of functional subregions in other brain disorders. Due to the method's ease and reliability, detection of somatotopic subregions may become useful for preoperative mapping in neurosurgery as well as for the postoperative assessment of surgical outcome.

An unexpected finding of the present study was the differences between functional connectivity maps before and after performing a task. While these effects did not affect the validity of parcellation, they might be interpreted within the context of brain plasticity, such as the one shown after e.g., motor training (Taubert *et al.*, 2011). The assessment of neuroplasticity effects using rs-fMRI, may prove helpful for the evaluation of rehabilitation after focal brain lesions. To apply rs-fMRI in clinical studies with patients after stroke or head trauma seems a realistic goal for the near future.

Summary

Dissertation zur Erlangung des akademischen Grades

Dr. rer. med.

<u>Parcellation of the human sensorimotor cortex: a resting-state fMRI study</u>

eingereicht von: Xiangyu Long

angefertigt am Max-Planck-Institut für Kognitions- und Neurowissenschaften

betreut von Prof. Dr. Arno Villringer und Dr. Daniel S. Margulies

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The somatosensory cortex is a brain region with distinct, yet related, functional and anatomical components; the primary motor cortex (MI), responsible for motor control, and the primary somatosensory cortex (SI), responsible for integrating relevant somatosensory information. In human populations, this region has traditionally been identified by the histological features of postmortem brains (e.g., BAs, Brodmann, 1909; Vogt. & Vogt., 1919; Economo, 1926; Sanides, 1970). More specifically, according to Brodmann's cytoarchitecture atlas, MI is located in BA4, and SI is found throughout BA1, 2, and 3 (Vogt. & Vogt., 1919).

While histological studies have proven invaluable in understanding cortical structure, in order to understand more of the dynamic, functional properties of the human brain, in-vivo studies must be performed which are based on functional properties. By using electrical stimulation on the cortical surface, for example, Penfield and colleagues found a degree of functional specialization of the cortex which was unavailable to histological analysis (Penfield & Boldrey, 1937; Okada et al., 1984). While these approaches have proven reliable in the discovery of functional and structural parcellation in the past, such approaches are prohibitively invasive. They are also remarkably time intensive, and would never be capable of analyzing whole populations of individuals, and a complete understanding the cortical variances across individuals would be similarly implausible.

Because understanding the structural and functional properties of the sensorimotor cortex is necessary for understanding human development and disease (Taubert et al., 2011, Sehm et al., 2014), there are clear benefits to developing non-invasive approaches to parcellate these brain regions according to their function. Different neuroimaging modalities have been employed to this end, namely functional connectivity (FC) analysis of functional Magnetic Resonance Imaging (fMRI) data, which estimates the temporal correlation of Blood Oxygen Level Dependency (BOLD) signals between brain regions (Friston et al., 1993; Biswal et al., 1995; Cordes et al., 2000; Hampson et al., 2002; Hampson et al., 2004; Fransson, 2005; Fox & Raichle, 2007).

More recently, resting state functional Magnetic Resonance Imaging (rs-fMRI) has been identified as a highly promising method for implementing a task-free approach to parcellating cortical structures according to their functions. Resting state data provides several key advantages over task-based analysis, namely that ease of acquisition allows for inclusion of broader populations and task-free approaches allow for the production of data that can be used to explore multiple hypotheses. To date, subregions of the somatosensory cortex have already been parcellated by rs-fMRI. These data demonstrate that hand or mouth regions, for example, present patterns similar to the activation regions detected via task-based fMRI (Schubotz *et al.*, 2010; Wig *et al.*, 2014). These previous studies reported, however, did not provide any validation of the reported (presumable somatotopic) arrangement (Nebel et al., 2014).

The present thesis begins at this juncture, and aims to determine whether the subregions discerned through rs-fMRI data are consistent with the somatotopic arrangement of those body parts. For this purpose, rs-fMRI scans were acquired and participants also performed a motor-task in order to obtain cerebral activation areas corresponding to different body parts (i.e., hand, foot and tongue). We hypothesized that the subregions based on rs-fMRI data corresponded to the functional somatotopic arrangement as identified by task-based fMRI.

In order to cover MI and SI, in the present study BA 3 and 4 were selected, as this allowed for the best fit across all participants. Task-induced activity regions of body parts were detected by the general linear model. The subregions within BA 4 and BA 3 were detected by functional connectivity-based parcellation analysis. The

subregions from rs-fMRI corresponded spatially to a somatotopic representation of upper-middle-lower limb segmentation, as identified by task-based fMRI. By quantitative comparison, a high correspondence between task-based subregions and the rs-fMRI subregions was detected on both group level and individual level.

Interestingly, the resting-state parcellation map demonstrated higher correspondence to the task-based divisions after individuals performed the motor tasks. This finding is novel and may reflect an immediate plasticity effect. However, the precise physiological meaning of this post-task effect on resting-state connectivity maps remains unclear at present and has to be investigated in the future. The relationships between different body parts were investigated. The ipsilateral right foot-hand and hand-tongue showed similar correlation values, which were both higher than the foot-tongue relationship. The foot-tongue presented no significant correlations.

There are several directions this line of research may explore in the future. First, rs-fMRI may be used to detect even more fine-scale features of the somatosensory cortex (e.g., sites of the digits within the hand area). This work requires high spatial resolution of the fMRI data, precise generation of the activity maps (Sanchez-Panchuelo et al., 2012), and would allow for the creation of a functional somatotopic atlas. Second, it seems highly promising to combine rs-fMRI with other magnetic resonance imaging methods for delineating Brodmann areas within the sensorimotor cortex in order to achieve a structural/functional parcellation. And third, there is a clinical/neurological perspective: The hope is that the approach presented in this thesis can be used to detect alterations of brain organization in patients and also the effects of therapies.

In summary, this PhD thesis presented a parcellation analysis of the sensorimotor cortex with resting-state fMRI data, validating the results with in-session task-based motor activities. The results confirmed that the somatotopic organization of upper-middle-lower body parts can be detected via resting-state fMRI data. Another finding, novel to the neuroscience community, was an observed post-task effect on resting state connectivity. Future work will be dedicated to detecting finer structures within the somatosensory cortex, working towards a somatotopic map, combining rs-fMRI with other parcellation approaches to achieve a

structural/functional parcellation, and exploring the clinical/neurological application of the present thesis.

Article included in the present thesis:

Long X, Goltz D, Margulies DS, Nierhaus T, Villringer A. Functional connectivity-based parcellation of the human sensorimotor cortex. European Journal of Neuroscience (impact factor in 2013: 3.75). 2014 Apr; 39(8):1332-42. doi: 10.1111/ejn.12473. Epub 2014 Jan 13.

Presentation included in the present thesis:

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Erklärung über die eigenständige Abfassung der Arbeit

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren.

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As the first author:

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Thank you for your reading!