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Regional structural differences across functionally parcellated Brodmann areas of human primary somatosensory cortex

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ABSTRACT

Ultra-high-field (UHF) MRI is ideally suited for structural and functional imaging of the brain. High-resolution structural MRI can be used to map the anatomical boundaries between functional domains of the brain by identifying changes related to the pattern of myelination within cortical gray matter, opening up the possibility to study the relationship between functional domains and underlying structure in vivo. In a recent study, we demonstrated the correspondence between functional (based on retinotopic mapping) and structural (based on changes in T_2^*-weighted images linked to myelination) parcellations of the primary visual cortex (V1) in vivo at 7 T (Sanchez-Panchuelo et al., 2012b). Here, we take advantage of the improved BOLD CNR and high spatial resolution achievable at 7 T to study regional structural variations across the functionally defined areas within the primary somatosensory cortex (S1) in individual subjects. Using a traveling wave fMRI paradigm to map the internal somatotopic representation of the index, middle, and ring fingers in S1, we were able to identify multiple map reversals at the tip and base, corresponding to the boundaries between Brodmann areas 3a, 3b, 1 and 2. Based on high resolution structural MRI data acquired in the same subjects, we inspected these functionally-parcellated Brodmann areas for differences in cortical thickness and MR contrast measures (magnetization transfer ratio (MTR) and signal intensity in phase sensitive inversion recovery (PSIR) images) that are sensitive to myelination. Consistent area-related differences in cortical thickness and MTR/PSIR measurements were found across subjects. However these measures did not have sufficient sensitivity to allow definition of areal boundaries.

Introduction

Ultra-high-field (UHF) MRI is ideally suited to structural imaging of the brain as it allows the spatial resolution of MRI studies to be increased to a level where it is possible to identify changes in the pattern of myelination within the cortical gray matter. Myelin is the major source of T_1 and magnetization transfer (MT) contrast, and also contributes to T_2^* contrast (Langkammer et al., 2012; Sanchez-Panchuelo et al., 2012b). These MR contrasts are enhanced at UHF, facilitating the visualization of myelo-architectural features. Recent high field MR studies have shown excellent in vivo visualization of the variation of myelin content within gray matter, based on T_1 contrast at 7 T (Geyer et al., 2011), the ratio of T_1/T_2 contrast at 3 T (Glasser and Van Essen, 2011) and T_1/T_2^* contrast at 7 T (De Martino et al., 2012).

Cortical architectonic regions are identified by the thickness and composition of their laminae; although cortical areas have been classically defined by cytoarchitectonic analysis in post-mortem brains, as in the definition of Brodmann maps (Brodmann, 1909), there is a great degree of concordance between structural parcellations of the cortex based on differences in the distribution of cell bodies, cytoarchitecture, and those maps based on differences in myelination, myeloarchitecture (Vogt and Vogt, 1919). One example is the primary visual cortex – cytoarchitectonically referred to as Brodmann's area 17 – which can be distinguished from neighboring regions by the presence of a dense band of myelination in layer IV — the Stria of Gennari. Lamination patterns within the gray matter on MR images of the striate cortex correlate with the pattern of myelination (Clark et al., 1992; Eickhoff et al., 2005) and cytoarchitecture (Eickhoff et al., 2005) observed in histology. In primary somatososensory cortex, which is cytoarchitectonically subdivided into four Brodmann areas (3a, 3b, 1 and 2), cortical fields corresponding to cyotoarchitectonic areas 3a, 3b and 1 have also been identified based on their myelin content in the marmoset (Krubitzer and Kaas, 1990) and macaque (Disbrow et al., 2003) using light-field photomicrographs of manually flattened stained for myelin cortex. In humans, a recent study comparing post-mortem T_1-weighted MR images to myelin-stained sections demonstrated a myeloarchitectonic difference between Brodmann area 4 of the motor cortex and area 3a of the primary somatosensory cortex (Geyer et al., 2011). Similarly, differences in overall

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regional myelination within the primary somatosensory cortex may be resolvable with MRI, thus allowing cortical parcellation to be carried out in vivo using anatomical images.

The ability to visualize the detailed cortical myeloarchitecture in vivo provides a method by which to map the boundaries between functional and anatomical domains of the brain directly in vivo. Thus, the correlation of brain function and underlying structure has been demonstrated in striate primary visual cortex, V1 (Bridge et al., 2005; Sanchez-Panchuelo et al., 2012b) and extra-striate visual area, V5 (Walters et al., 2003). Besides the visual cortex, the primary somatosensory cortex and primary auditory cortex have also been characterized as having high myelin content in both the macaque (Bock et al., 2009) and human brain (Cohen-Adad et al., 2012; Deistung et al., 2013; Glasser and Van Essen, 2011; Sigalovsky et al., 2006). These areas also exhibit a topographic organization that can be mapped using fMRI. In the primary somatosensory cortex (S1), the well established, medio-lateral somatotopic organization of the finger representations (Francis et al., 2000; Nelson and Chen, 2008; Sanchez-Panchuelo et al., 2010; Schweizer et al., 2008; Stringer et al., 2011) is shared across the four areas of S1, impeding the identification of these sub-regions based on maps reflecting finger representation. However, primate studies show that the representations of the proximal-to-distal surface of each finger in the different sub-regions form mirror images of one another (Kaas et al., 1979; Merzenich et al., 1978; Nelson et al., 1980), providing a way to identify Brodmann areas within S1 from functional maps alone. Functional identification of these areas in vivo in single human subjects has proven problematic until recently. However, using 7 T fMRI in conjunction with traveling-wave, vibrotactile stimulations along the length of the index finger, we have demonstrated the functional parcellation of all four distinct Brodmann areas of S1 in individual human subjects (Sanchez-Panchuelo et al., 2012a).

Here we investigate the correlation between functionally-parcellated areas within human primary somatosensory cortex (S1) and the underlying anatomical structure in the same subjects in vivo. We extend the traveling wave paradigm by stimulating three fingers (index, middle and ring fingers) rather than a single finger, in order to define the functional boundaries of areas 3a, 3b, 1 and 2 over a greater extent of S1. We then investigate regional differences of the underlying structure across these functionally-defined Brodmann areas based on high resolution magnetization transfer ratio (MTR) and phase sensitive inversion recovery (PSIR) image data acquired in the same individuals. Since both PSIR and MTR are myelin-sensitive MR measures, we hypothesize that signal intensity in MTR and PSIR maps will reflect variations in the pattern of myelination within the different functionally defined regions of primary somatosensory cortex. We provide an estimate of myelination by averaging each of these measures over profiles across the depth of the gray matter. In addition we investigate the variation in cortical thickness over these functionally defined areas, since variations in cortical thickness correlate with differences in cell type (Geyer et al., 1999) and may also be associated with borders between distinct cortical areas (Brodmann, 1909; von Economo, 1929).

Methods

Four subjects experienced in fMRI experiments participated in this study (age 30.8 ± 5.4, 1 female). The study was approved by the University of Nottingham Medical School Research Ethics Committee and all subjects gave full written consent. Scanning was performed at 7 T using a volume, bird-cage transmit coil and a 32-channel receive coil (Nova Medical, Inc., Wilmington, MA). Each subject participated in two scan sessions: one functional session and one structural session. For myelin measurements and cortical unfolding we used cortical segmentations based on whole head anatomical data with 1 mm isotropic resolution previously acquired at 3 T for each subject who participated in this study.

Functional imaging

Stimuli and paradigm

Vibrotactile stimuli were delivered to the index, middle and ring fingers of the left hand using nine, independently-controlled MR-compatible piezoelectric devices positioned at the proximal (base), middle and distal (tip) phalanges of each finger (Fig. 1). Each stimulator delivered a supra-threshold (~100 μm amplitude) 30 Hz vibrotactile stimulus to ~1 mm^2 of the glabrous skin of each site (Dancer Design, St Helens, United Kingdom, http://www.dancerdesign.co.uk).

The vibrotactile stimuli were presented using two orthogonal versions of a traveling wave (TW) paradigm; a 'between-digit' TW paradigm designed to generate a traveling wave of activity across the somatotopic representation of the fingers in S1 (Sanchez-Panchuelo et al., 2010) and a 'within-digit' TW paradigm to produce mirrored maps of the representations of the proximal-to-distal surfaces of these fingers in S1 (Sanchez-Panchuelo et al., 2012a). In the 'between-digit' TW paradigm, each finger was sequentially stimulated (at all three phalanges simultaneously) from the index to the ring finger in turn (Fig. 1*A*). In an analogous fashion, for the 'within-digit' TW paradigm stimuli were applied sequentially from the proximal to distal phalanges (to the three digits simultaneously) (Fig. 1*B*). Each location was stimulated for 8 s (sixteen 0.4 s blocks of continuous stimulation, separated by 0.1 s gaps to limit adaptation). One cycle of stimulation across the 3 locations therefore took 24 s. Each fMRI run consisted of 8 cycles of stimulation, resulting in a total duration of 192 s. Stimuli were delivered in either a forward (index to ring, proximal to distal) or backward order (ring to index, distal to proximal). Four fMRI runs were performed using the between-digit traveling wave paradigm and six fMRI runs using the within-digit traveling wave paradigm (an increased number of runs were used for the within-digit TW paradigm to improve the statistical power of this measure).

Functional data acquisition

Functional data were obtained using multi-slice, single shot gradient echo (GE), echo-planar imaging (EPI) with the following parameters:

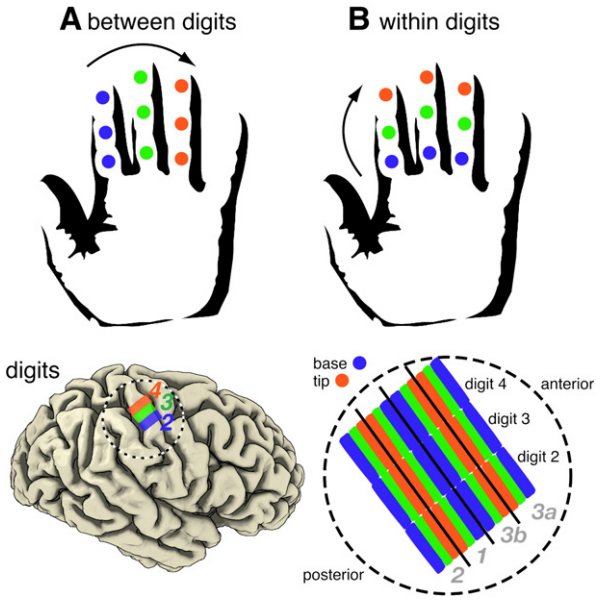

Fig. 1. Schematic depiction of the traveling-wave experimental paradigms. *A*. Traveling wave paradigm used to localize index, middle and ring finger representations. Digits are sequentially stimulated either from index to ring, or in the reverse order, to produce a traveling wave of activity within the cortical representations of the digits in S1. *B*. Traveling wave paradigm used to assess within-digit somatotopy: The index, middle and ring fingers are stimulated sequentially either from the base to the tip or in the reverse order. The expected map is orthogonal to the representation of the digits themselves, with phase reversals at the border of the Brodmann sub-areas of S1.