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Human brain atlas for automated region of interest selection in quantitative susceptibility mapping: Application to determine iron content in deep gray matter structures☆

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ABSTRACT

The purpose of this paper is to extend the single-subject Eve atlas from Johns Hopkins University, which currently contains diffusion tensor and T_1-weighted anatomical maps, by including contrast based on quantitative susceptibility mapping. The new atlas combines a "deep gray matter parcellation map" (DGMPM) derived from a single-subject quantitative susceptibility map with the previously established "white matter parcellation map" (WMPM) from the same subject's T_1-weighted and diffusion tensor imaging data into an MNI coordinate map named the "Everything Parcellation Map in Eve Space," also known as the "EvePM." It allows automated segmentation of gray matter and white matter structures. Quantitative susceptibility maps from five healthy male volunteers (30 to 33 years of age) were coregistered to the Eve Atlas with AIR and Large Deformation Diffeomorphic Metric Mapping (LDDMM), and the transformation matrices were applied to the EvePM to produce automated parcellation in subject space. Parcellation accuracy was measured with a kappa analysis for the left and right structures of six deep gray matter regions. For multi-orientation QSM images, the Kappa statistic was 0.85 between automated and manual segmentation, with the inter-rater reproducibility Kappa being 0.89 for the human raters, suggesting "almost perfect" agreement between all segmentation methods. Segmentation seemed slightly more difficult for human raters on single-orientation QSM images, with the Kappa statistic being 0.88 between automated and manual segmentation, and 0.85 and 0.86 between human raters. Overall, this atlas provides a time-efficient tool for automated coregistration and segmentation of quantitative susceptibility data to analyze many regions of interest. These data were used to establish a baseline for normal magnetic susceptibility measurements for over 60 brain structures of 30- to 33-year-old males. Correlating the average susceptibility with age-based iron concentrations in gray matter structures measured by Hallgren and Sourander (1958) allowed interpolation of the average iron concentration of several deep gray matter regions delineated in the EvePM.

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Abbreviations: AIR, Automated Image Registration; Amg, Amygdala; CC, Corpus Callosum; CCb, Body of the Corpus Callosum; CCg, Genu of the Corpus Callosum; CCs, Splenium of the Corpus Callosum; CN, Caudate Nucleus; CSF, Cerebrospinal Fluid; COSMOS, Calculation of Susceptibility through Multiple Orientation Sampling; CX, Cortex; DGMPM, Deep Gray Matter Parcellation Map (derived from QSM calculations); DN, Dentate Nucleus; ETAAS, Electro-thermal Atomic Absorption Spectroscopy; EvePM, "Everything" Parcellation Map with gray and white matter ROIs; EC, External Capsule; GM, Gray Matter; GP, Globus Pallidus; GRE, Gradient Recalled Echo; Hip, Hippocampus; IC, Internal Capsule; INAA, Instrumental Neutron Activation Analysis; LDDMM, Large Deformation Diffeomorphic Metric Mapping; LSQR, Algorithm for sparse linear equations and sparse least squares; LVL, Lateral Ventricle; MEDI, Morphology Enabled Dipole Inversion; MRI, Magnetic Resonance Imaging; PT, Putamen; QSM, Quantitative Susceptibility Mapping; Put, Putamen; RN, Red Nucleus; ROI, Region of Interest; RSO, Regularized Single Orientation; SHARP, Sophisticated Harmonic Artifact Reduction for Phase data; SN, Substantia Nigra; SS, Sagittal Stratum; TH, Thalamus; Th, Thalamus; TKD, Thresholded K-space Division; TR, Thalamic Radiations; WKD, Weighted K-space partial Derivatives; WM, White Matter; WMPM, White Matter Parcellation Map (derived from previous T_1-weighted and DTI measurements).

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Introduction

Stereotaxic atlases provide a useful frame of reference when analyzing subject data, especially when automated coregistration between subject and atlas allows for efficient segmentation of the subject brain into regions of interest from the atlas. The most commonly used atlases for MRI research contain information that is based mainly on cytoarchitectural features derived from T_1-weighted contrast. For example, the Talairach and Tournoux atlas (Talairach and Tournoux, 1988) showcases Brodmann's areas, while the International Consortium of Brain Mapping (ICBM) provides a target template for normalization-based group analyses (Mazziotta et al., 1995, 2001).

The Eve atlas from Johns Hopkins University is a single-subject female brain at 1 mm^3 isotropic resolution, in standard Montreal Neurological Institute (MNI) coordinates (Mori et al., 2008, 2009; Oishi et al., 2009). Regions of interest (ROIs) in the White Matter Parcellation Map (WMPM) based on this atlas contain information about white matter orientation and tract structures that is derived from Diffusion Tensor Imaging. However, they provide limited detail on gray matter structures, which have a very low fractional anisotropy (Mori et al., 2008). The resolution from DTI is relatively low at 3 T, with large 2.2 mm^3 isotropic voxels (10.6 μL). Previously, these gray matter structures were delineated using T_1-weighted anatomical scans (Oishi et al., 2009); however, several gray matter structures, such as the red nucleus, substantia nigra, and dentate nucleus, were not easily visible on T_1-weighted images.

With the recent advent of high-field imaging, quantitative susceptibility mapping (QSM) provides a novel contrast, particularly in deep gray matter regions (de Rochefort et al., 2010; Deistung et al., 2008; Duyn et al., 2007; X. Li et al., 2012; Liu, 2010; Liu et al., 2009, 2012; Schweser et al., 2011; Shmueli et al., 2009; Wharton and Bowtell, 2010). Magnetic susceptibility is the intrinsic property of a substance to affect an applied magnetic field (Kuchel et al., 2003; Schenck, 1996; Yablonskiy, 1998). This susceptibility can be calculated using a map of the resonance frequency in each voxel, which traditionally utilizes the MR signal phase from gradient-recalled echo (GRE) imaging. The origin of contrast in QSM images has been attributed to iron-containing structures in the deep gray matter nuclei and myelin-containing structures in white matter, the latter being orientation-dependent (Fukunaga et al., 2010; Haacke et al., 2010; Lee et al., 2009, 2010; Li et al., 2011, W. Li et al., 2012; X. Li et al., 2012; Liu, 2010; Schweser et al., 2011). While all susceptibilities in tissue are diamagnetic due to the large water content (Schenck, 1996), iron-rich structures such as the red nucleus and globus pallidus appear bright in a quantitative susceptibility map referenced to CSF, indicating that they are more paramagnetic with respect to CSF, whereas white matter structures appear dark, indicating relative diamagnetism with respect to CSF.

Here, we used high resolution multi-orientation QSM images (1.7 μL voxels) to create a new deep gray matter parcellation map (DGMPM), which is expected to be useful as a template for automated group analyses that can anatomically identify iron-rich structures in the brain. We then combined this map with the white matter regions from the previously established White Matter Parcellation Map (WMPM) from the Eve Atlas to create the EvePM, the "Everything Parcellation Map in Eve Space." Our goal is to provide a normal baseline of mean magnetic susceptibility for each region, which can be correlated with brain iron concentration, and, when such data are or become available, can be compared with various neurodegenerative diseases, in hopes of finding a biomarker (Bilgic et al., 2012; Schenck and Zimmerman, 2004). The Eve atlas, complete with maps displaying different T_1-weighted, diffusion-based, and susceptibility contrasts, as well as parcellation maps, can be freely obtained from the MRI Studio website (http://www.mristudio.org), with additional information on the website for the National Research Resource for Functional Brain Imaging (http://www.mri-resource.kennedykrieger.org).

Methods

MRI acquisition

After IRB approval and written informed consent, five healthy male volunteers (aged 30 to 33 years old) were studied at 3 Tesla (Philips Medical Systems, Best, The Netherlands) using dual-channel body-coil excitation and 32-channel head coil receive. In order to generate high-quality quantitative susceptibility maps, we acquired a multi-orientation dataset from each subject (X. Li et al., 2012; Liu et al., 2009; Wharton and Bowtell, 2010). Each volunteer was scanned with the brain positioned in four separate orientations with respect to the scanner's B_0 field: in the supine position, with the head parallel to the direction of the scanner's B_0 field; tilted to the right, with the subject's right ear towards the right shoulder; tilted back, with cushions under the subject's neck so that the chin was tilted up; and tilted to the left and slightly forward, with the subject's left ear towards the left shoulder and the chin tilted forward towards the chest. When positioning the imaging volume, the midline of the sagittal plane was placed parallel to an imaginary line connecting the anterior (AC) and posterior commissures (PC) of the corpus callosum, and the midlines of the coronal and axial planes were positioned along the medial longitudinal interhemispheric fissure.

Each orientation data set consisted of one survey scan, a reference scan for SENSE reconstruction (Pruessmann et al., 1999), a T_1-weighted MPRAGE (Mugler and Brookeman, 1990), and a 3D gradient-recalled echo. The MPRAGE scan was acquired to display structural detail, using a 3D gradient-recalled echo with a turbo-field echo readout (TFE factor = 184, TFE shot interval = 3500 ms, TI = 1000 ms, SENSE = 1 × 1 × 2, TE = 3.2 ms, TR = 7.0 ms, $\alpha = 8^o$, Scan Duration = 4:53 min) with an acquired isotropic resolution of 1.2 mm^3 (120 slices, FOV =220 mm × 220 mm × 144 mm, reconstructed to 224 mm × 224 mm). Phase images were acquired using a 3D ten-echo gradient-recalled echo sequence (SENSE =2 × 1 × 2, TR = 70 ms, TE_1 = 6 ms, ΔTE = 6 ms, $\alpha = 20°$, Scan Duration = 9:19 min), with a nominal resolution of 1.2 mm^3 isotropic, covering the entire brain (120 slices, FOV =220 mm × 220 mm × 144 mm, reconstructed resolution =0.98 mm × 0.98 mm × 1.2 mm). Fat suppression was accomplished using a water-selective ProSet 121 excitation pulse and one 60 mm-wide REST slab positioned inferior and parallel to the acquired volume. Complex images from the 32 coils were combined using standard SENSE reconstruction on the system. Single-orientation QSM images were calculated using the GRE images acquired in the supine position.

Analysis of multi-orientation and single-orientation quantitative susceptibility maps

We followed a protocol to derive quantitative susceptibility maps using multiple orientations described previously by X. Li et al. (2012). For each subject, the fourth-echo magnitude images acquired at all orientations were coregistered to the fourth-echo magnitude image acquired in the supine position, using the Oxford FMRIB Software Library (FSL) Linear Image Registration Tool (FLIRT) (Jenkinson and Smith, 2001; Smith et al., 2004; Woolrich et al., 2009), with rigid-body linear transformation with a cost ratio determined by a normalized mutual information algorithm. In principle, any magnitude image acquired at any of the echo times can be used to coregister the images from the orientations; in this particular case, the fourth-echo magnitude images (acquired at TE = 24 ms) were used because they exhibited excellent contrast between brain structures and the area outside the brain, while maintaining sufficient signal. The coregistration transformation matrix was applied to the real and imaginary data from every echo time (TE) to generate coregistered real and imaginary images, which were subsequently converted to magnitude and phase images. Therefore, the data from all of the orientations were placed in the same frame of reference with respect to the subject, particularly with

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