NeuroImage 171 (2018) 176–189

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

# Longitudinal atlas for normative human brain development and aging over the lifespan using quantitative susceptibility mapping

Yuyao Zhang [a,1], Hongjiang Wei [a,1], Matthew J. Cronin [a], Naying He [b], Fuhua Yan [b], Chunlei Liu [a,c,*]

[a] Electrical Engineering and Computer Science, University of California at Berkeley, CA, USA
[b] Department of Radiology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China
[c] Helen Wills Neuroscience Institute, University of California at Berkeley, CA, USA

A B S T R A C T

Longitudinal brain atlases play an important role in the study of human brain development and cognition. Existing atlases are mainly based on anatomical features derived from T1-and T2-weighted MRI. A 4D developmental quantitative susceptibility mapping (QSM) atlas may facilitate the estimation of age-related iron changes in deep gray matter nuclei and myelin changes in white matter. To this end, group-wise co-registered QSM templates were generated over various age intervals from age 1–83 years old. Registration was achieved by combining both T1-weighted and QSM images. Based on the proposed template, we created an accurate deep gray matter nuclei parcellation map (DGM map). Notably, we segmented thalamus into 5 sub-regions, i.e. the anterior nuclei, the median nuclei, the lateral nuclei, the pulvinar and the internal medullary lamina. Furthermore, we built a "whole brain QSM parcellation map" by combining existing cortical parcellation and white-matter atlases with the proposed DGM map. Based on the proposed QSM atlas, the segmentation accuracy of iron-rich nuclei using QSM is significantly improved, especially for children and adolescent subjects. The age-related progression of magnetic susceptibility in each of the deep gray matter nuclei, the hippocampus, and the amygdala was estimated. Our automated atlas-based analysis provided a systematic confirmation of previous findings on susceptibility progression with age resulting from manual ROI drawings in deep gray matter nuclei. The susceptibility development in the hippocampus and the amygdala follow an iron accumulation model; while in the thalamus sub-regions, the susceptibility development exhibits a variety of trends. It is envisioned that the newly developed 4D QSM atlas will serve as a template for studying brain iron deposition and myelination/demyelination in both normal aging and various brain diseases.

## Introduction

The course of normal human brain development and aging provides a foundation for the understanding of pathological brain degeneration. As such, longitudinal magnetic resonance imaging (MRI) atlases play an important role in understanding the evolution of human brains. The most commonly used atlases for MRI research are mainly based on anatomical features derived from T1-and T2-weighted images. For example, the well-known International Consortium of Brain Mapping (ICBM) atlas (Collins et al., 1995; Mazziotta et al., 2001) and the Talairach atlas (Talairach and Tournoux, 1988; Lancaster et al., 2000) both provide target T1-weighted templates for normalization-based group analysis. T2-weighted MRIs are commonly used for fetus and neonate atlas construction (Serag et al., 2012; Shi et al., 2014; Wei et al., 2016a,b).

Quantitative susceptibility mapping (QSM) provides a novel contrast, particularly in iron-rich deep-brain nuclei and white matter fiber bundles (Deistung et al., 2008; de Rochefort et al., 2010; Liu, 2010; Wharton et al., 2010; Liu et al., 2012; Carpenter et al., 2016; Wei et al., 2016a,b). This is attributed to the sensitivity of QSM to the spatial variations of molecular or cellular components that exhibit different magnetic susceptibility properties. As indicated by several recent studies (Shmueli et al., 2009; Haacke et al., 2010), magnetic susceptibility of the human brain is mainly influenced by iron and myelin. Human brain myelination and iron deposition evolve over the whole lifespan (Hallgren and Sourander, 1958; Lebel et al., 2012), which is a critical factor in the characterization of early-life brain development and also in the recognition of normative and pathological brain evolution in later-life (Lotfipour et al., 2012).

Although there have been susceptibility atlases proposed for certain age groups (Lim et al., 2013), a longitudinal statistical atlas constructed from the general healthy population based on QSM is still lacking. Registering brains of subjects across the whole lifespan to a common atlas is currently not practical due to large variations in tissue contrast and brain anatomy. For various neurological and psychiatric studies based on

* Corresponding author. Electrical Engineering and Computer Science, University of California at Berkeley, 505 Cory Hall, MC #1770, Berkeley, CA 94720, USA.
*E-mail address:* chunlei.liu@berkeley.edu (C. Liu).
[1] These authors contributed equally to the work presented in this paper.

https://doi.org/10.1016/j.neuroimage.2018.01.008
Received 7 October 2017; Accepted 5 January 2018
Available online 8 January 2018

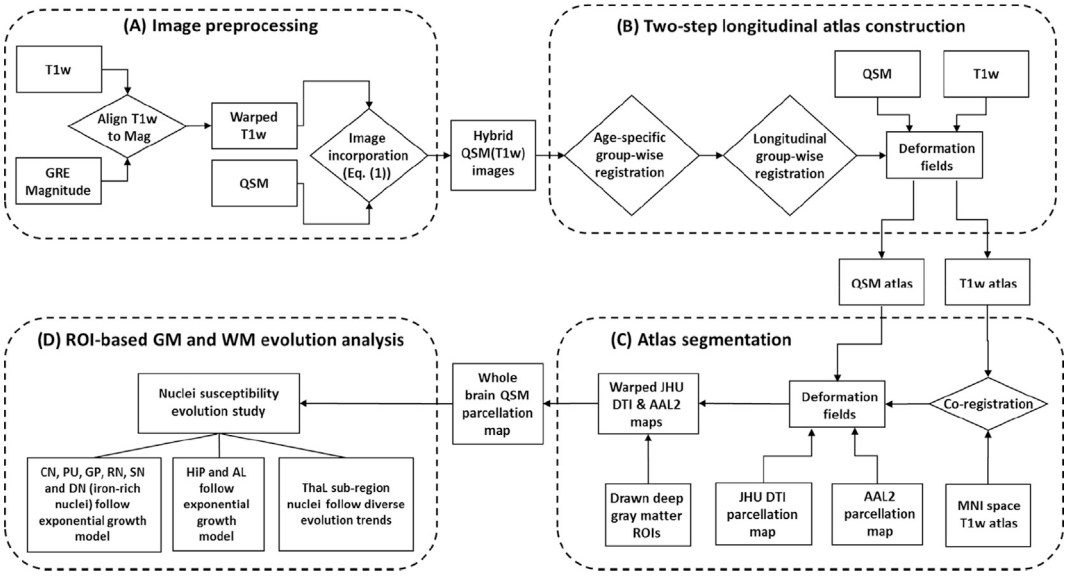


**Fig. 1.** Flow chart of 4D QSM atlas construction and brain nucleus magnetic susceptibility analysis.

iron-rich deep gray matter nuclei, automated co-registration between subject and atlas allows efficient segmentation of the subject brain into regions of interest (ROI) from the atlas. Yet, the existing studies on QSM for aging and neurological disorders are based on group-wise quantitative analysis in a few manually annotated regions of interests (ROIs) (Li et al., 2014; He et al., 2015). A robust common QSM template throughout lifespan is greatly needed.

Hence, in the present work, we create a longitudinal QSM atlas using image registration guided by novel fused QSM and T1-weighted images. These two types of contrast are complementary as T1 provides excellent contrast between cortical gray white matter while QSM provides excellent contrast in the iron-rich deep gray matter (Hanspach et al., 2017). By generating group-wise co-registered age-specific brain atlases over various intervals from ages 1–83 years, a longitudinal atlas was generated by co-registering age-specific atlases across different age intervals.

Based on the proposed atlas, we created an accurate deep gray matter nuclei parcellation map (DGM map), which includes 9 regions of interest: the dentate nucleus (DN), red nucleus (RN), substantia nigra (SN), caudate nucleus (CN), putamen (PU), globus pallidus (GP), hippocampus (HiP), amygdala (AL) and thalamus (Thal). The thalamus was further segmented into 5 sub-regions, i.e. the anterior nuclei, the median nuclei, the lateral nuclei, the pulvinar and the internal medullary lamina. Finally, we built the "whole brain QSM parcellation map" of 204 ROIs, by combining AAL2 brain parcellation (Rolls et al., 2015), JHU DTI-based white-matter atlases (Mori et al., 2005), and the proposed DGM map. This proposed whole brain parcellation map allowed automated and accurate segmentation of gray matter and white matter structures for the analysis of QSM data.

## Methods

An overview of the procedure for the 4D atlas construction and whole-brain ROI-based magnetic susceptibility analysis is presented in Fig. 1.

### *Longitudinal atlas construction*

#### *Data acquisition and reconstruction*

A total of 166 healthy subjects (74 M/92 F) with an age range of 1–83 years old were included in the study. The subjects were scanned either at the Brain Imaging and Analysis Center (BIAC) at Duke University, using a 3T scanner (MR 750, GE Healthcare, Milwaukee, WI), or at Rui Jin Hospital (Shanghai, China), using a 3T scanner (Signa HDxt, GE Healthcare, Milwaukee, WI). Imaging was carried out with approval of the institutional review board and informed consent from the adult subjects and parental consent for babies. Conventional T1-weighted images with 1 mm isotropic resolution were acquired to display brain structure. Thereafter, a three-dimensional multi-echo gradient echo (GRE) sequence was utilized to obtain T2*-weighted images with the following scan parameters:

The 8 infant subjects (age 1–2 years, 4M/4F) were scanned using a GE MR750 3T with echo time (TE) = 40 ms, repetition time (TR) = 50 ms, and an original spatial resolution of $1 \times 1 \times 1\ mm^3$. Infants were scanned without being sedated and were fed before scanning. Neonatal earmuffs were used for hearing protection, and possible motion artifacts were mitigated by immobilization with a cotton pillow. An experienced neonatologist and a neuroradiologist were in attendance throughout the imaging process. A pulse oximeter was used to monitor heart rate and oxygen saturation. The 22 children (age 2–10 years, 8M/14F) subjects were scanned using a GE MR750 3T with $TE_1$/spacing/$TE_8$ = 5/2.94/25.6 ms, TR = 55 ms, and an original spatial resolution of $0.6 \times 0.6 \times 1.5\ mm^3$. The 19 teenage (age 11–20 years, 10M/9F) subjects were scanned using a GE MR750 3T scanner with $TE_1$/spacing/$TE_8$ = 4/2.82/29.4 ms, TR = 41 ms, and an original spatial resolution of $0.86 \times 0.86 \times 2\ mm^3$. The 117 adults (age 21–83 years, 52M/65F) subjects were scanned on a GE Signa HDxt 3T scanner with $TE_1$/spacing/$TE_8$ = 5.468/3/26.5 ms, TR = 54.6 ms, and an original spatial resolution of $0.86 \times 0.86 \times 2.0\ mm^3$.

As the imaging protocols and scanners employed varied among the scans, all the images were resampled to the same spatial resolution of $1 \times 1 \times 1\ mm^3$ through operations in k-space in order to minimize the impact of the varying scan parameters.

QSM reconstruction was performed in STI Suite V3.0 (https://people.eecs.berkeley.edu/~chunlei.liu/software.html). The sum of squares of GRE magnitude images across echo times ($\sum_{i=1}^{p} mag_i^2$, $i = 1, 2, \ldots, p$, where $p$ is the number of echoes), was used to mask and extract the brain tissue using the brain extraction tool (BET) in FSL (Smith et al., 2004). The raw phase was unwrapped using a Laplacian-based phase unwrapping (Schofield and Zhu, 2003; Li et al., 2011). The normalized phase $\psi$ was calculated as: $\psi = \frac{\sum_{i=1}^{n} \omega_i}{\gamma \mu_0 H_0 \sum_{i=1}^{n} TE_i}$ where ω is the unwrapped phase. The normalized background phase was removed with the spherical mean value (SMV) method (Schweser et al., 2011; Wu et al., 2012). The variable radius of the SMV filter increased from 1 pixel at the brain boundary