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Segmenting and validating brain tissue definitions in the presence of varying tissue contrast

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ABSTRACT

We propose a method for segmenting brain tissue as either gray matter or white matter in the presence of varying tissue contrast, which can derive from either differential changes in tissue water content or increasing myelin content of white matter. Our method models the spatial distribution of intensities as a Markov Random Field (MRF) and estimates the parameters for the MRF model using a maximum likelihood approach. Although previously described methods have used similar models to segment brain tissue, accurate model of the conditional probabilities of tissue intensities and adaptive estimates of tissue properties to local intensities generates tissue definitions that are accurate and robust to variations in tissue contrast with age and across illnesses. Robustness to variations in tissue contrast is important to understand normal brain development and to identify the brain bases of neurological and psychiatric illnesses. We used simulated brains of varying tissue contrast to compare both visually and quantitatively the performance of our method with the performance of prior methods. We assessed validity of the cortical definitions by associating cortical thickness with various demographic features, clinical measures, and medication use in our three large cohorts of participants who were either healthy or who had Bipolar Disorder (BD), Autism Spectrum Disorder (ASD), or familial risk for Major Depressive Disorder (MDD).

We assessed validity of the tissue definitions using synthetic brains and data for three large cohort of individuals with various neuropsychiatric disorders. Visual inspection and quantitative analyses showed that our method accurately and robustly defined the cortical mantle in brain images with varying contrast. Furthermore, associating the thickness with various demographic and clinical measures generated findings that were novel and supported by histological analyses or were supported by previous MRI studies, thereby validating the cortical definitions generated by the proposed method: (**1**) Although cortical thickness decreased with age in adolescents, in adults cortical thickness did not correlate significantly with age. Our synthetic data showed that the previously reported thinning of cortex in adults is likely due to decease in tissue contrast, thereby suggesting that the method generated cortical definitions in adults that were invariant to tissue contrast. In adolescents, cortical thinning with age was preserved likely due to widespread dendritic and synaptic pruning, even though the effects of decreasing tissue contrast were minimized. (**3**) The method generated novel finding of both localized increases and decreases in thickness of males compared to females after controlling for the differing brain sizes, which are supported by the histological analyses of brain tissue in males and females. (**4**) The proposed method, unlike prior methods, defined thicker cortex in BD individuals using lithium. The novel finding is supported by the studies that showed lithium treatment increased dendritic arborization and neurogenesis, thereby leading to thickening of cortex. (**5**) In both BD and ASD participants, associations of more severe symptoms with thinner cortex showed that correcting for the effects of tissue contrast preserved the biological consequences of illnesses. Therefore, consistency of the findings across the three large cohorts of participants, in images acquired on either 1.5T or 3T MRI scanners, and with findings from prior histological analyses provides strong evidence that the proposed method generated valid and accurate definitions of the cortex while controlling for the effects of tissue contrast.

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1. Introduction

Precisely segmenting brain tissue as either gray matter (GM) or white matter (WM) in anatomical MR images of the brain is essential for accurately measuring various brain features, such as the thickness of the cortical mantle [1]. These measures represent the characteristics of brain tissue that are the end product of developmental processes that shape the brain in health and in illness and that therefore permit the in vivo study of both normal brain development and aberrant development that produces neurological and neuropsychiatric illnesses [2–8]. However, the presence of noise, partial volume effects, variations in tissue intensities and contrast with age [9], and nonuniformities in tissue intensities that derive from inhomogeneous B1 fields introduce errors in the tissue segmentations. Therefore, methods for accurate tissue segmentation must be robust to these sources of error.

Some of the presently available methods for tissue segmentation are reasonably robust to the presence of noise and intensity inhomogeneities. These methods typically model the distribution of tissue intensities as a mixture of Gaussian distributions, and they apply a method for Expectation Maximization (EM) [10] to estimate the mean and variance of the Gaussian distributions while maximizing the likelihood of the observed data. These methods have been extended to estimate and correct for intensity inhomogeneities simultaneously while segmenting tissues [10] and are robust to the initial estimate of tissue definitions [11]. However, in the presence of salt-and-pepper, white noise these methods label isolated WM voxels as GM and GM voxels as WM. These errors are mitigated by other prior methods that model the spatial distribution of tissue intensities as a Markov Random Field (MRF) that imposes the constraint that brain regions must consist of a homogeneous tissue type [12]. Several other methods use k-nearest neighbor (kNN) [13], Fuzzy clustering [14], or Bayesian MRF/EM based formulation [15] to generate a probabilistic tissue segmentations [16]. The performance of these methods is typically evaluated by visual inspection of the tissue definition and by comparing quantitatively the statistics of segmented tissues with those for tissue segmented either by other methods and subsequently edited by a human expert, or using a computer-generated brain with known tissue definitions. Although these prior methods have differing mathematical formulations, their performances on real-world datasets have been similar, with no one method performing significantly better than others [17].

Noise and partial volume effects, as well as variations in tissue contrast, can significantly influence performance of the prior methods for tissue segmentation. One of the major sources of variation is the spatial variation in B1 excitation and refocusing pulses, which produces inhomogeneous excitation of the protons within and across homogeneous tissues. Inhomogeneous excitations in turn lead to variations in signal intensity and tissue contrast for a specified pulse sequence parameters. While, the effects of inhomogeneous tissue intensities on segmentation can be minimized by homogenizing tissue intensities across a brain either by first estimating the spatial variation in signal intensity and then correcting them using algorithms such as N3 [18] and N4ITK [19], or by simultaneously estimating intensity inhomogeneities and delineating brain tissue [10]. However, these methods cannot account for the effects of variations in tissue contrast on tissue definitions across participant brains.

These methods can help to correct B1-based inhomogeneities in signal intensities, but they cannot account for the variations in tissue contrast that derive from the biological processes that influence tissue contrast and the validity of tissue segmentation, such as spatial variations in the myelin content of white matter (WM), iron content in deep gray matter (GM) nuclei, and water content across both tissue types [9]. These biological influences on signal intensity and tissue contrast can also change with age or vary across illnesses and healthy participants, thereby altering the definitions of GM and WM in the brain and important measures that depend on those definitions, such as cortical thickness. We have previously shown using synthetic, real-world data, and mathematical derivations that commonly used platforms for tissue segmentation define thinner cortices in brain images that have lower tissue contrast. [9] Furthermore, age related changes in tissue water content decreases tissue contrast with age, thereby biasing the existing methods to define thinner cortex in brains of increasing ages [9,20,21]. Investigators have assumed that the age-related thinning of the cortical mantle that has been reported across numerous studies represent only age-related changes in the cellular and histological features that define differing tissue types in the brain, such as the density of neuronal cell bodies, dendrites, synapses and other neuropil components of GM or the axons and myelin of WM [22]. But that is an incorrect assumption. A substantial portion of age-related thinning of the cortical mantle as defined using contrast-based segmentation of tissues on MR images derive from age-related changes in water and other biological variables that are unrelated to those cellular features, including neuropil and axons, that define GM and WM. Similarly, abnormalities reported across diagnostic groups in measures of cortical thickness could derive simply from illness-related differences in water, myelin, or iron content that influences tissue contrast without representing differences across groups in the cellular features that define GM and WM. A method for tissue segmentation is needed that accurately accounts for variations in tissue contrast and generates more valid definitions of tissues and the brain measures that depend on them, such as cortical thickness.

Our proposed method for tissue segmentation models the spatial distribution of intensities as a Markov Random Field (MRF) in order to impose the constraint that the brain consists of various homogeneous tissues, similar to previous methods [12]. Our method maximizes the likelihood of the observed data using an Expectation Maximization (EM)-based algorithm that estimates the parameters in the MRF formulation. It uses an accurate mathematical formulation for the conditional probabilities in the MRF model and adapts the parameters to the distribution of local tissue intensities. Unlike the existing methods [23–27] that locally adapt only the mean intensities to distributions of local image features, we adapted both the average and variance of the tissue intensities generating accurate tissue definitions that are robust to local variations in tissue intensities. MRI does not have resolution and/or contrast to define brain tissues determined by its cellular and molecular features. However, tissue segmentation methods that are invariant to tissue contrast and water content would generate tissue definitions that are valid representations of cellular and molecular features that define brain tissue. Our results showed that adapting parameters to local distribution of tissue intensities and using accurate mathematical formulations generate tissue definitions that are robust to variations in tissue contrast. We visually and quantitatively compare the performance of our method with those of prior methods, including one based on the histogram of voxel intensities and another that uses prior formulation of conditional probabilities in MRF model of tissue intensities without adaptive adjustment of estimated parameters. We validate the segmentations of the cortical mantle defined using our method by assessing their accuracy in simulated brains in which the ground truth is known and in real-world brain images of several hundred participants are either healthy and who have Bipolar Disorder (BD), Autism Spectrum Disorder (ASD), or familial risk for Major Depressive Disorder (MDD). We expect that the proposed method would account for the variations in tissue contrast while segmenting brain tissue and