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Fusion of white and gray matter geometry: A framework for investigating brain development

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ABSTRACT

Current neuroimaging investigation of the white matter typically focuses on measurements derived from diffusion tensor imaging, such as fractional anisotropy (FA). In contrast, imaging studies of the gray matter oftentimes focus on morphological features such as cortical thickness, folding and surface curvature. As a result, it is not clear how to combine findings from these two types of approaches in order to obtain a consistent picture of morphological changes in both gray and white matter.

In this paper, we propose a joint investigation of gray and white matter morphology by combining geometrical information from white and the gray matter. To achieve this, we first introduce a novel method for computing multi-scale white matter tract geometry. Its formulation is based on the differential geometry of curve sets and is easily incorporated into a continuous scale-space framework.

We then incorporate this method into a novel framework for "fusing" white and gray matter geometrical information. Given a set of fiber tracts originating in a particular cortical region, the key idea is to compute two scalar fields that represent geometrical characteristics of the white matter and of the surface of the cortical region. A quantitative marker is created by combining the distributions of these scalar values using Mutual Information. This marker can be then used in the study of normal and pathological brain structure and development. We apply this framework to a study on autism spectrum disorder in children. Our preliminary results support the view that autism may be characterized by early brain overgrowth, followed by reduced or arrested growth (Courchesne, 2004).

1. Introduction

The brain consists of diverse structures, each with a characteristic shape and an intricate architecture. Their shape varies across the normal population, and is an important feature thought to reflect genetic and environmental factors that influence both normal and pathological neurodevelopment (e.g., Mangin et al., 2010; Toga and Thompson, 2003). Thus, the shape of brain structures is of importance in a variety of neuroscience applications.

The morphology of the cortical surface has been studied extensively, with a variety of studies focusing on geometrical properties of the cortex such as folding, curvature, thickness and surface area (see, e.g., Mangin et al., 2010 for an extensive review). The shape of subcortical gray matter structures has also been the topic of numerous studies (e.g., Bouix et al., 2005; Gao et al., 2012; Styner et al., 2006). However, little is known about macrostructural white matter morphology and geometry. Typically, neuroimaging investigations of white matter focus on diffusion tensor imaging (DTI) measures such as fractional anisotropy (FA), mean, radial and axial diffusivities computed at each voxel. These measures are typically assumed to reflect levels of axonal organization, myelination, or white matter integrity. However, these biological interpretations are being increasingly questioned (e.g., Jones et al., 2013). Furthermore, such DTI measures are not directly informative on the geometry of the white matter tracts.

Thus, in order to achieve a complete morphological characterization of the brain, it is not clear how to combine voxel-level DTI measures of the white matter (such as FA), with the macrostructural geometry features typically used in shape analyzes of the cortex

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and other gray matter structures. This highlights a need for methods that facilitate a joint analysis of gray and white matter morphology, in order to better understand the developmental and pathological processes that impact the brain. For example, the importance of neuronal migration and axonal outgrowth in the development of the brain is well-known, and so is the fact that genetic and environmental factors disrupting these mechanisms may result in neurological disease (e.g., Mcintosh et al., 2008; Métin et al., 2008; Rakic, 1988; see also Section 7). Such neurodevelopmental processes are likely to have an impact on both white matter geometry and cortical surface geometry, and this motivates the need for imaging markers that can capture and quantify the geometrical relationship between gray and white matter structures.

To address this need, we introduce here a method for computing multi-scale white matter geometry, based on the differential geometry of curve sets. We then incorporate this method into a framework that investigates the geometrical relationship between white matter tracts and the cortical areas they connect to. This relationship has not been extensively studied, despite the existence of several theories linking cortical development and function to the development of white matter and its geometrical structure (e.g., Van Essen, 1997).

While it may be self-evident that the geometry of the white matter and that of the gray matter must somehow be related, it is not currently known what the precise relationship is. Deriving explicit formulas that link cortical folding with the spread and curvature of white matter fibers is a highly challenging task that would require extensive knowledge of brain tissue biomechanics. Therefore, as an alternative, we propose here an approach based on information theory. Given a set of fiber tracts which connect to a particular cortical region of interest (ROI), we first apply our novel method to compute the geometry of the tracts, represented as a field of scalars defined over the tracts. Independently, we also compute a second scalar field over the cortical ROIs, a which represents a geometrical characteristic of the surface at each point, such as its mean curvature, folding index, thickness, or many others. We then capture the relationship between the two scalar fields via Mutual Information. This type of approach is general, in that it can be applied with any scalar characteristics of the gray and the white matter. It also avoids the need to specify one-to-one correspondences between individual fibers and specific points on the cortex, as such correspondences are inherently unstable and depend on various parameters and tractography algorithm specifics.

This article is organized as follows. First, we review the current state of the field. We then introduce our method for scale-based geometrical analysis of white matter tracts. Following this, we present our framework for combining gray and white matter geometrical information. As an illustration, we apply this framework to a study that investigates the course of age-related changes during childhood in typical development and in autism spectrum disorder (ASD). This preliminary study is focused on a single cortical region. Nevertheless, it shows how our methods can be applied to reveal potential developmental differences between healthy children and children with ASD. In particular, our results support the view that autism may involve a period of early brain overgrowth (from birth to approx. four years of age), followed by a period of reduced or arrested growth (Courchesne, 2004), warranting an investigation into a larger sample using our method.

2. Previous work

2.1. White matter geometry

Standard features from the differential geometry of surfaces have been widely used in the medical image community in order to quantify cortical surface geometry. Such features include functions of the surface's principal curvatures, e.g. the mean curvature (defined as the mean of the principal curvatures), the Gaussian curvature (defined as the product of the principal curvatures), the shape index or the curvedness (Awate et al., 2010; Koenderink and van Doorn, 1992). However, a lot less work has been done on the geometry of white matter fibers. In the diffusion MRI community, the *sub-voxel* geometry of fibers has been defined using the diffusion-weighted signal (e.g. Kaden et al., 2007; Zhang et al., 2011), or based on neighborhood regularization (e.g. Ramírez-Manzanares et al., 2007; Savadjiev et al., 2008). However, for the purposes of the present work, we need larger scale *macrostructural* white matter geometry features, i.e. features that span more than a single voxel.

Methods for macrostructural white matter geometry analysis in diffusion MRI typically compute the curvature and torsion of *individual* fibers recovered with a tractography algorithm (e.g., Batchelor et al., 2006). The geometry of *sets* of curves is usually obtained by mapping individual curves to medial axes/surfaces (e.g. Yushkevich et al., 2008) or an average representation (e.g., Corouge et al., 2006; O'Donnell and Westin, 2007). However, this type of mapping may involve heuristic decisions about the choice of corresponding points and fiber similarity measures. An elegant alternative was recently introduced on the basis of the currents framework (Vaillant and Glaunès, 2005), which represents fiber tracts as a smooth vector field and captures global tract shape while avoiding the need for specific point correspondences (Durrleman et al., 2009).

All geometric analysis methods based on fiber tractography share the limitations of the underlying tractography algorithm. Tractography methods typically depend on multiple parameters and may not always produce stable and reproducible results. Recognizing this limitation, a method for computing white matter geometry indices directly from diffusion imaging data was proposed in our earlier work (Savadjiev et al., 2010). This method computes gradients of the diffusion tensor field within a 3D neighborhood, without any prior knowledge about fiber tracts. This is an advantage, as it avoids tractography and its limitations. On the other hand, this advantage comes at a price: the geometry of all the white matter present in the 3D neighborhood is represented by a single scalar, which may be less informative when distinct fiber populations pass near each other.

In the present work, we introduce a scale-based white matter geometry analysis method that works with the tangent vector field of tracts obtained by tractography. This reliance on tractography is a limitation, but it also allows the analysis of a specific tract independently of the influence of other nearby tracts. Furthermore, no constraints are imposed on the underlying model of diffusion, this new method can be used with high quality HARDI data. Finally, instead of computing a single scalar representing fiber dispersion at a point, we compute *directional* dispersion in a "dispersion distribution function", as detailed below. These two methods therefore exploit the two sides of a basic trade-off: avoiding the uncertainty inherent in tractography (Savadjiev et al., 2010), versus exploiting information about tract structure provided by tractography, as proposed here.

As for a comparison with the currents-based approach of Durrleman et al. (2009), this latter method is optimized to capture global tract shape and its modes of variation in a population. In contrast, our method computes local geometrical features based on the differential geometry of curve sets, which makes possible subsequent tract-based statistical analysis with methods such as Yushkevich et al. (2008). We note, however, that our method is complementary to the currents framework of Durrleman et al. (2009), and both may be used in conjunction in order to analyze the geometry of a currents vector field.