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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 [7].

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Keywords

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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., [32,51]). 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., [32] for an extensive review). The shape of subcortical gray matter structures has also been the topic of numerous studies (e.g., [4,16,50]). 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., [24]). 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 analyses of the cortex 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., [33,35,40]; 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., [56]).

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, 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 [7], 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 [2,26]. 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. [25,60], or based on neighborhood regularization (e.g. [42,46]). 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., [3]). The geometry of *sets* of curves is usually obtained by mapping individual curves to medial axes/surfaces (e.g. [59]) or an average representation (e.g., [6,36]). 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 [55], which represents fiber tracts as a smooth vector field and captures global tract shape while avoiding the need for specific point correspondences [13].

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 [47], without requiring prior tractography. This method, however, is currently only defined for the single tensor model of diffusion, itself with well known limitations in regions of complex white matter structure, such as areas with fiber crossings.

In the present work, we introduce a scale-based white matter geometry analysis method that is an intermediate approach between the tensor gradient method of [47], and vector field based methods such as the currents method [13]. While our proposed method is based on vector fields derived from tractography and is therefore subject to all associated limitations, its advantage with respect to [47] is that it is not limited by the tensor model of diffusion, and also allows for a more precise characterisation of fiber fanning at different (macrostructural) spatial scales, as detailed in Section 2.1.1. As for the currents method of [13], it 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 [59]. We note, however, that our method is complementary to the currents framework of [13], and both may be used in conjunction in order to analyze the geometry of a currents vector field.

2.1.1 Comparison to tensor-based model of dispersion—Both our method and the method of [47] compute macrostructural white matter geometry. However, they approach this problem in diametrically opposed ways, which makes them complementary to each other. The method of [47] works directly with DTI data 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 contrast, our new method 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. Unlike the method of [47], defined only for diffusion tensor fields, our method can be used even 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. The two methods therefore exploit the two sides of a basic trade-off: avoiding the

uncertainty inherent in tractography [47], versus exploiting information about tract structure provided by tractography, as proposed here.

2.2 Fusing information between white and gray matter geometry

As mentioned earlier, most *in vivo* neuroimaging investigations of white matter have focused on diffusion tensor imaging (DTI) measures defined at each voxel, such as fractional anisotropy (FA), mean, radial and axial diffusivities (see [53] for a recent review in the context of autism). As this type of information is non-geometrical, it is not clear how to combine it with morphological findings in the gray matter (GM) expressed in terms of surface area, curvature, thickness, etc.

Possibly as a result of this discrepancy, the problem of mapping white matter properties onto cortical geometry has not been widely investigated. In [37], tractography information is used to help determine corresponding points on the cortical surface of different subjects. More recently, [52] define correspondence between WM tracts and GM locations by extending the tract in a straight line from the tip of the tract to the boundary of the cortex. This approach is rather heuristic, and does not take into account the complexity of the structure of the cerebral cortex structure that often causes axons to bend upon entering the gray matter [34]. In [19], an atlas estimation methodology is developed based on the current framework [55] for estimating the variability of both curves and surfaces.

In [1], the authors avoid the necessity to specify an explicit correspondence between white matter voxels and cortical surface locations. They detect correlated reductions in FA and cortical thickness in neurodegenerative diseases by using sparse canonical correlation analysis (SCCA). SCCA is an unsupervised multivariate analysis technique which automatically detects mutually predictive, anatomically distributed regions across different imaging modalities, in this case the FA image over the white matter, and the cortical thickness image over the gray matter. This makes it an appealing approach for detecting correlated networks in disjoint modalities, with no prior hypothesis of anatomical association between the two. In the present article, however, we are solving a different problem, and SCCA is not directly applicable. We are interested in combining geometry information from grey and white matter regions that are anatomically connected, as opposed to finding anatomically distributed networks based on correlation.

3 Multi-scale white matter geometry

The work in [49] (recently extended with an application to heart myofibers in [48]) models white matter fibers as sets of dense, locally parallel 3D curves called ‘streamline flows’, and represents them as a frame field [38], obtained by associating with every point along each 3D curve an orthonormal frame (E_T, E_N, E_B) . Here E_T is the curve’s tangent vector, and E_N and E_B represent the normal and binormal vectors, respectively. An example of such a frame at a point along a curve is the standard Frenet frame [38], illustrated schematically in Fig. 1. The geometry of the streamline flow can then be characterized, *with respect to the local frame*, by computing three *curvature functions*, measuring the rate of change of the tangent vector in the frame’s three orthonormal directions [48,49]. Essentially, these curvature functions measure the bending of the flow in these three directions.

As diffusion MRI data is potentially noisy and reflects a variety of tissue properties other than pure fiber geometry, the authors of [48,49] compute the three curvature functions indirectly. This is done by inferring a regularizing model (defined as a generalized helicoid) from the diffusion MRI data, that is parametrized by the three curvature functions. This is a solution of the inverse problem, i.e., the inference of streamline flow geometry from incomplete information present in the diffusion MRI data.

In this paper, we present a solution for the forward problem, i.e., computing the curvature functions directly from the fiber tracts, as opposed to using diffusion imaging data directly. The forward problem is important, given the abundance of streamline representations of fiber tracts and the increasing interest in the analysis of their shape. The forward problem also presents a somewhat different set of challenges. On the one hand, determining the standard Frenet curvature of streamlines (the tangential curvature of [48,49]) is trivial, since by construction streamlines are continuous in their tangential direction. On the other hand, the Frenet frame field of a curve is not defined along straight line segments, and curve inflection points cause discontinuities in the orientation of the normal and binormal vector fields, which makes the interpretation of bending in the normal and binormal directions difficult in practice.

In this work, we propose to measure the rate of change of the tangent vector E_T not only in the direction of the normal E_N and the binormal E_B , but in *all* directions in the plane orthogonal to E_T . This alleviates the need to define Frenet frames, which can be very unstable for the reasons specified above. Furthermore, while the Frenet frame directions are sufficient to capture the geometry for slowly varying sets of curves, such as the cardiac myofibers in [48], brain white matter tracts can change their orientation quite rapidly, even within a local neighborhood. Thus, by computing the rate of change of E_T along the entire circle orthogonal to E_T , instead of only 2 directions, we ensure against missing “interesting events”, and we describe comprehensively the complex geometry of brain white matter tracts.

By capturing the variation of curve orientation in directions orthogonal to the curves, we quantify the extent to which the fibers deviate from being parallel - or “disperse” - and we characterize their pattern of dispersion. The authors of [47] define a scalar measure of dispersion computed from diffusion tensor data, which corresponds to the total amount of white matter dispersion within a local neighborhood. In contrast, here we compute at each point along a fiber a function on a circle that reflects the dispersion in all directions on that circle. One can think of this function as a 2D “dispersion distribution function” (DDF), i.e. a function whose values are proportional to the amount of fiber dispersion in each direction orthogonal to the fiber. This function provides a richer description of dispersion than the scalar measure of [47], and constitutes our first main contribution. As mentioned earlier, computing the standard Frenet curvature of continuous curves is trivial and will not be considered here.

3.1 Problem Statement

Our method is a high-level analysis that is applied *after* tractography. Thus, we assume the particular tractography method has already been tested on synthetic data or phantoms, and

its limitations are known. The focus of the experiments in this paper is therefore on the macrostructural geometric analysis of already-traced fiber tracts, as opposed to the particular tractography algorithm.

The goal of our method is the following: given a set $\mathcal{C}$ of streamlines (curves) C_i that represent the output of some streamline tractography algorithm, with a tangent vector E_T defined at each point $\mathbf{p}$ on each curve $C_i \in \mathcal{C}$, we compute the function

$$\Psi(\theta) = \nabla_{\mathbf{v}} E_T. \quad (1)$$

Here $\nabla_{\mathbf{v}} E_T$ represents the covariant derivative of the tangent vector E_T in direction $\mathbf{v}$, with the constraints that $\{\mathbf{v} | \mathbf{v} \in \mathcal{S}^1 \cap \mathbf{v} \perp E_T\}$, i.e., $\mathbf{v}$ is a direction on the unit circle centered at $\mathbf{p}$ in the plane orthogonal to E_T , and is denoted by angle θ in this plane. This function is computed at each $\mathbf{p}$ along each C_i , resulting in a DDF at each $\mathbf{p}$ describing the local fiber dispersion pattern relative to the local tangent vector E_T , as illustrated in Fig. 2 (left).

We note that (1) is defined only for continuous vector fields. That is, a line passing through point $\mathbf{p}$ on curve C_i with direction $\mathbf{v}$ must always intersect another curve C_j at point $\mathbf{p}'$ with a tangent vector E'_T defined at $\mathbf{p}'$, otherwise $\nabla_{\mathbf{v}} E_T$ will not exist. Since we work with a vector field $F = \cup E_T$ of tangent vectors of 1D curves in 3D Euclidean space $\mathbb{R}^3$, F is not continuous, specific point correspondences cannot always be established and (1) is not always defined.

To resolve this issue, we adopt an approach akin to Parzen window estimation with a uniform kernel. Specifically, we construct a continuous vector field $F^c(x, y, z)$ at each $(x, y, z) \in \mathbb{R}^3$ by averaging F over a neighborhood $\mathcal{N}$ centered at (x, y, z) :

$$F^c(x, y, z) = \frac{1}{N} \sum_{(i,j,k) \in \mathcal{N}} F_{(i,j,k)} \quad (2)$$

where $\mathcal{N}$ is some neighborhood of $\mathbb{R}^3$ centered at location (x, y, z) , and N is the number of vectors of F that occur within $\mathcal{N}$.

We note that F is discrete because it is obtained from a discrete set of curves, but also because of the discrete nature of diffusion MRI data, which causes each curve C_i not to be continuous, but rather a polyline approximation to a continuous curve. Each C_i is therefore a sequence of small linear segments, with one tangent vector E_T per segment. There is thus a countable number of vectors belonging to F in each neighborhood $\mathcal{N}$, which allows the summation in (2). The spatial location of these vectors is denoted with the (i, j, k) subscript in (2), which are floating point coordinates with sub-voxel resolution.

We also note that *a priori*, the tangent vectors can be presented either as E_T or as $-E_T$. To avoid arbitrary sign changes from one location to the next which can drastically affect the result of (2), we ensure a sign consistency over the entire dataset relative to a global coordinate frame, such as that derived from the principal components of the tracts' spatial distribution.

3.2 Scale space

Since we seek to characterize the variation of curve orientation in directions orthogonal to the curves, in our implementation we choose the neighborhood $\mathcal{N}$ to be shaped as a *disk* lying in the plane orthogonal to E_T , with a small thickness chosen to be 1 voxel. The radius of this disk is treated as a scale parameter. To compute (1) for a given direction $\mathbf{v}$ at a given location $\mathbf{p}$, we first apply (2) at $\mathbf{p}$ in order to obtain a value for E_T at scale S , E_T^S . Then, we apply (2) at location $\mathbf{p} + S\mathbf{v}$ (i.e., at a distance S from $\mathbf{p}$ in direction $\mathbf{v}$), in order to obtain a value for the tangent vector $E_T'^S$ at location $\mathbf{p} + S\mathbf{v}$.

Note that the definition of $\Psi(\theta)$ given in equation (1) implies via the use of the covariant derivative symbol $\nabla_{\mathbf{v}}$ the computation of angular changes in E_T over infinitesimally small displacements in direction $\mathbf{v}$.

The definition of $\Psi(\theta)$ in equation (1) makes use of the covariant derivative symbol $\nabla_{\mathbf{v}}$, which implies computation of angular changes of E_T over infinitesimally small displacements in direction $\mathbf{v}$. Since in practice we compute angular changes in E_T over finite length distances S , to avoid notational abuse we introduce the following approximation:

$$\Psi(\theta) = \nabla_{\mathbf{v}} E_T \approx \Delta_{\mathbf{v}} E_T^S = \Psi^S(\theta). \quad (3)$$

This definition of Ψ at scale S , or Ψ^S , makes explicit the fact that we do not compute actual derivatives, but rather changes in vector orientation over distance S in direction $\mathbf{v}$.

In practice, we compute $\Psi^S(\theta)$ as the angular difference between E_T^S and $E_T'^S$:

$$\Psi^S(\theta) = \Delta_{\mathbf{v}} E_T^S = \arccos \left(\left\langle E_T^S, E_T'^S \right\rangle \right), \quad (4)$$

with $\langle \cdot, \cdot \rangle$ denoting the standard dot product in $\mathbb{R}^3$. Thus, the units of Ψ^S are in radians.

These steps are illustrated in Fig. 2 (right). The inclusion of a scale parameter in this manner allows for a simple way to construct a *continuous* scale space.

3.2.1 Total Dispersion (TD)—The computation of $\Psi^S(\theta)$ at each fiber point is carried over a range of θ values, i.e. over a discretization of the unit circle. This results in a vector-valued DDF, which is not trivial to visualize. To facilitate the visualization and interpretation of the DDF, in the following we will work with the mean of the DDF at a given point. This “projects” the vector-valued DDF to a single scalar quantity. We will refer to the mean of the DDF as the Total Dispersion (TD) measure.

3.3 Examples

In order to illustrate these concepts, we now present a few examples of the above analysis applied to a few representative fiber tracts. At this point, these figures are intended only for illustration purposes. For full technical details on data acquisition and the tractography algorithm, please see Section 5 below.

As described previously, our method computes DDFs at each point along each curve in the tract set. In order to summarize this large amount of information and present it visually, in the following figures we show fibers where each point is colored by the measure of total dispersion (TD), such that yellow indicates high TD values.

In Fig. 3, we show the TD measure for a set of fibers passing through the corpus callosum. Here TD was computed with a scale parameter $S = 5\text{mm}$. In this particular set of callosal tracts, as the fibers leave the body of the corpus callosum they disperse towards different parts of the cortex. Not surprisingly, it is at these locations that we observe the highest TD values. This example serves to illustrate one of the differences between this new method and the tensor gradient based method of [47]. The latter is based on the tensor model of diffusion, which cannot reliably capture lateral callosal projections due to the presence of fiber crossings. In contrast, the HARDI-based tractography method used here allows to trace the full extent of callosal projections, which then permits the analysis of their geometry.

We next explore the effect of varying the scale parameter S on a fiber tract which connects the substantia nigra of the brain stem to the caudate nucleus, a sub-cortical grey matter structure. This tract was selected for illustration purposes because it presents a well-defined fanning structure.

In Fig. 4, we present views of this tract colored by TD, computed at scales S ranging from 1.7mm to 10.2mm. Please refer to Section 3.2 above for a definition and discussion of the concept of scale. At the smallest scale only very local dispersion features are highlighted. With increasing scale, the larger fanning structure is highlighted more strongly, while small features are progressively lost. As an anatomical reference, we overlay this on the T1 volume which has been registered to DWI space (this results in some blurring of the T1 image as a by-product of registration).

4 Fusion of white matter geometry with cortical surface geometry

Up to here, our approach can be summarized with the following two steps, which we have just described, namely 1) performing tractography to define the white matter tracts of interest; and 2) computing the geometry of these tracts. We next augment our pipeline with two additional steps:

- 3 Computing the geometry of the cortical regions the tracts connect to.
- 4 Quantifying the relationship between the geometry of white matter and that of gray matter via Mutual Information.

All these steps are summarized in Fig. 5, and the latter two are detailed below.

4.1 Cortical surface geometry (step 3)

To characterize cortical surface geometry, we first extract the GM/WM boundary surface using *FreeSurfer*. FreeSurfer is a freely available software toolbox which reconstructs mesh-based models of the boundary between white matter and cortical gray matter, as well as the pial surface [10,14]. Once these surfaces are reconstructed, a set of anatomical measures are then computed at each mesh vertex, including surface curvature. In addition, FreeSurfer

allows the parcellation of the cortex into neuroanatomical areas, using both the geometrical model of the cortical surface and neuroanatomical convention [15]. For more information, please consult <http://surfer.nmr.mgh.harvard.edu/>.

In our framework, the FreeSurfer parcellation was registered to the diffusion MRI space to allow for cortical ROIs to be used as extraction masks for the tractography. However, please note that all cortical curvature computations are performed in the original FreeSurfer space, to avoid the introduction of registration artifacts.

As an illustration, we show in Fig. 6 the fibers connecting to the *pars orbitalis* region in the right hemisphere, colored by the TD value at each point. Note the ‘bottleneck’ with low TD (yellow/red), and the fibers’ dispersion towards the cortex (green/blue). We overlay these fibers onto a volume representing the mean curvature of the GM/WM boundary surface. To create this visualization, the mean curvature values were rasterized into a 3D volume with the `mri surf2vol` utility (part of the FreeSurfer toolkit). The resulting volume was then registered to the diffusion MRI space (which gives a thickness to the surface as a by-product). As an anatomical reference, we also show the fibers overlaid on the T1 image.

4.2 Mutual Information (step 4)

The above preprocessing steps give, at each point along the fiber tract of interest, a scalar quantifying the dispersion of the tract at that point. In addition, at each point on the cortical surface ROI, we have a scalar quantifying the mean curvature (or possibly another feature) of the surface at that point. The probability density functions (pdf) of these values can then be estimated, and the relationship between them captured via a quantity known as *Mutual Information* (MI) [9]. The MI between two random variables measures the amount of information they share. For example, a MI value of 0 indicates that they are independent. The higher the MI value, the more ‘dependent’ the variables are, i.e. the more knowledge we gain of one by knowing the value of the other. MI should not be confused with the correlation between two variables, which measures the strength of the linear relationship between them. MI is much more general, as it does not assume any particular form of relationship between the variables. MI has been widely used in medical imaging, in particular for image registration (e.g., [57]). In this work, the use of MI allows us to combine information between geometrical measures on the white matter and on the gray matter.

The Mutual Information of two continuous random variables X and Y is defined as follows [9]:

$$MI(X;Y) = \int_Y \int_X p(x,y) \log \left(\frac{p(x,y)}{p(x)p(y)} \right) dx dy, \quad (5)$$

where $p(x, y)$ is the joint probability density function of X and Y , and $p(x)$ and $p(y)$ are their respective marginal probability densities.

As discussed earlier, different geometry-based features can be used in describing the geometry of the cortical surface. To illustrate the concept of linking the distribution of scalar gray and white matter geometrical features via Mutual Information, in the experiments

below we chose to work with Mean Curvature (MC, see Section 2.1) as a geometrical feature of the cortical surface and TD as a feature of the white matter tract.

4.2.1 Computing Mutual Information—Given the MC measure at each surface mesh vertex, and the TD measure at each point along the white matter tract, we used kernel density estimation [5] to compute a probability density estimate for each of the two measures.

Then, to compute MI, we used the MILCA estimator [28], the code for which is available online at <http://www.klab.caltech.edu/~kraskov/MILCA/> (we used function `MIhigherdim`). This is a robust estimator of MI which does *not* require *a priori* knowledge of the joint density of the two variables. This is an important difference between the manner in which we compute MI, and its typical computation in the image registration literature. The latter usually requires explicit correspondence between two images to compute the pixel-based joint density. In our work, we do not compute MI between two images. Rather, we compute one probability density estimate for MC over the cortical area and another one for TD over the connecting white matter tract. We treat these two density estimates as two one-dimensional data vectors, and we then use the method of [28] to compute MI between them. Because of this, explicit pointwise correspondence between white matter and cortical locations is not required.

5 Experiments

In the present work, we apply our novel methods to observe the evolution of brain geometry in children diagnosed with ASD, as well as in normal controls. ASD has been characterized as a disorder in which the brain undergoes an early period of overgrowth, from birth to approximately age 4. This early period of excessive growth is then followed by abnormally slow or even arrested growth. For an extensive literature review, please refer to [7]. Thus, our hypothesis is that our MI based measure will reveal a difference in the trajectory of brain development with age.

We are interested here only in providing an illustration of how our framework can be applied to population studies in a clinical setting. Because of this, we focused our experiments on a single region of the inferior frontal gyrus (IFG), the *pars orbitalis*, which has been involved in semantic processing of language. We chose this region as the IFG and the *pars orbitalis* have been previously implicated in ASD (e.g., [43]) and other neurodevelopmental disorders. A larger scale analysis over the entire cortex is the topic of future work.

5.1 Subjects and Data Acquisition

Diffusion and structural MRI data were acquired from 25 healthy male controls (HC, age range: 6.4 – 13.9 years, mean: 9.9, std dev: 2.2) and 19 male autism spectrum disorder patients (ASD, age range: 6.4 – 13.3 years, mean: 10.1, std dev: 1.9). A t-test for difference in age between the two groups results in a p-value of 0.70.

All imaging was performed using a Siemens 3T Verio™ scanner with a 32 channel head coil. Structural images were acquired on all subjects using an MP-RAGE imaging sequence (TR/TE/TI = 19s/2.54ms/.9s, 0.8mm in plane resolution, 0.9mm slice thickness). In addition, A HARDI acquisition was also performed using a monopolar Stejskal-Tanner diffusion weighted spin-echo, echo-planar imaging sequence with the following parameters: TR/TE=14.8s/110ms, b=3000s/mm², 2mm isotropic resolution, and 64 gradient directions as well as two b0 images. The DW-MRI images for both acquisitions of each subject were then filtered using a joint linear minimum mean squared error filter for removal of Rician noise. Eddy Current Correction was then performed using registration of each DWI volume to the unweighted b0 image.

5.2 Processing Pipeline

We implemented steps 1–4 listed above in Section 4 and summarized schematically in Fig. 5.

To define the tracts of interest in step (1), we first computed whole-brain tractography using the multi-fiber tracking method of [31]. To compute whole brain tractography, we seeded all voxels with FA > 0.3. After all tracts were computed, we extracted the interhemispheric tracts connecting the *pars orbitalis* regions of the left and right hemisphere as defined by the FreeSurfer parcellation of the cortex. The tracts were then cut within 6 mm from the midsagittal plane.

The computation of TD (step 2) was then applied to the resulting tracts as described in Section 3. An example of these tracts for one subject is shown in Fig. 7. Fig. 6 also shows these tracts for a different subject. For each subject, we computed the mean TD at an empirically chosen scale $S=10\text{mm}$ over these tracts in each hemisphere. At each point, we computed $\Psi^S(\theta)$ along 20 directions $\mathbf{v}$ distributed uniformly on the unit circle.

Mean curvature (MC) was computed over the cortical area (step 3), followed by the computation of MI (step 4) as described in Section 4. For each subject and for its *pars orbitalis* regions in both hemispheres, we computed a probability density estimate of MC and TD, which were then given as input to the MI estimation method of [28]. The density estimate of MC was computed over the range -1.25 to 1.25 mm^{-1} divided in 1250 uniformly spaced bins. Similarly, the density estimate for TD was computed over the range 0 to 0.5 rad ($\approx 29^\circ$), also divided in 1250 uniformly spaced bins.

In the next section, we report results based on Mutual Information between MC and TD for the *pars orbitalis* in each hemisphere. In particular, we report its correlation with subject age. In the following, we let M represent the mutual information between TD and MC: $M \equiv \text{MI}(\text{MC}, \text{TD})$.

6 Results

In the healthy controls population, the correlation between subject age and M in the left hemisphere was not significant, so we focus here on the right hemisphere.

In the healthy control group, we obtained a significant Pearson correlation co-efficient between age and M , with $p=0.0484$. However, due to the presence of four apparent outliers, we also computed the correlation using a robust linear regression method, as implemented with the ‘robustfit’ Matlab routine. As it is less sensitive to the outliers, this robust correlation was more significant ($p=0.0103$). As for the ASD subjects population, we did not obtain a significant correlation ($p=0.55$ for the Pearson correlation, $p=0.63$ for the robust correlation), which may suggest that pathology alters the normal course of brain development. These results are shown in Fig. 8, where the lines indicate the robust regression fit for the HC group in blue and the ASD group in red.

As a control experiment, we correlated M with intra-cranial volume. There were no significant correlations ($p=0.25$ for the HC group, $p=0.97$ for the ASD group). Further, there were no correlations between age and intra-cranial volume ($p=0.38$ for the HC group, $p=0.21$ for the ASD group). In addition, we correlated M with the gray matter volume of the *pars orbitalis* region, as measured with FreeSurfer. Again, there were no significant correlations ($p=0.88$ for the HC group, $p=0.97$ for the ASD group). There were also no significant correlations between age and the gray matter volume of the *pars orbitalis* region ($p=0.22$ for the HC group, $p=0.57$ for the ASD group). Thus, the observed correlations in Fig. 8 are not likely to be driven by differences in intra-cranial volume or gray matter volume.

7 Discussion

We introduced the motivation and groundwork for a novel framework for the analysis of the relationship between white matter geometry and cortical surface geometry. This relationship may be informative in many contexts in neuroscience, such as the study of neurodevelopment or the progression of atrophy in neurodegenerative diseases. Our Mutual Information-based marker may be interpreted as indicative of the extent to which the geometrical structure of the white matter tract is predictive/informative about the geometrical structure of the cortical area it connects to, and vice versa.

To illustrate potential applications of our method, we conducted a study in ASD, and our results show that normal age-related changes in the brain may be altered by ASD pathology. Our study remains preliminary, and more work is warranted in order to fully understand its implications for autism. However, it may be informative to place our results in the context of other findings in ASD.

7.1 Functional implications

In the present paper, our experiments were focused on the *pars orbitalis* cortical region in both hemispheres and the fiber tracts that connect them. The *pars orbitalis* is part of the inferior frontal gyrus (IFG), which has been implicated in high level association functions including an important role in language. In the context of autism, language and the IFG have been topics of numerous studies. For example, [12] have recently found an important reduction in interhemispheric neuronal synchronisation between language areas (including the IFG) in toddlers with autism (aged 1 to 3.5 years). These results would suggest “weaker” interhemispheric communication between the implicated areas [12].

On the other hand, [44] have found an *increased* involvement of right hemisphere frontal regions in language tasks in toddlers with autism, aged 2 to 3 years. This abnormally high recruitment of the right hemisphere suggests the possibility of increased communication between left and right language regions. Interestingly, a similar increase in the involvement of right hemisphere language regions has been found in normal aging [54], where it was associated with normal age-related atrophy in left hemisphere language areas. These changes in the right hemisphere are hypothesized to occur in order to compensate for age-related loss in gray matter in left hemisphere language regions. This process might be analogous to the increased involvement of right hemisphere activity in toddlers with autism to compensate for abnormalities in normal language development, but at this point this is still only a matter of speculation.

The right IFG, however, plays a role not only in language. It has also been found to be important for inhibition and attentional control [21]. Thus, the increase in our measure M seen with age in typically developing children may also be related to the development of inhibition and attentional control skills. But again, all such interpretations remain in the realm of speculation.

These findings illustrate the importance of interhemispheric communication between language areas such as the IFG, and how autism may affect it. Our experiments targeted the geometrical aspect of the structural connectivity between these regions. In typical development, our findings suggest that at the age of 6, the geometrical structure of the gray matter in the right *pars orbitalis* has a relatively weak coupling to the geometrical structure of the white matter that connects it to the contralateral area. The strength of this coupling (as measured with our Mutual Information based measure M) is then seen to increase with age.

In contrast, this coupling is stronger in ASD children at age 6, but then it does not appear to evolve with age. In such children a “stronger” interhemispheric connection may develop earlier in age, possibly underlying a greater right hemisphere involvement as suggested by [44]. The evolution of this connection, however, does not appear to develop further after age 6. Numerous evidence suggests that autism is characterized by an period of an overall brain overgrowth at an early age (from 0 to 4 years) followed by a premature arrest of growth [7]. Our finding can be seen to support this broad view.

7.2 Parallels with structural brain maturation

From a neurobiological point of view, the central question would be the biological underpinnings of the geometrical coupling between gray and white matter. This question cannot be answered with imaging techniques alone, and lies in the realm of future work. However, current knowledge of neurodevelopment and brain morphogenesis can provide some cues to the reasons for this coupling.

It has long been recognized that during gestation, the development of the cortical folding pattern is influenced by axonal connections. The exact process through which this occurs, however, is still under debate. One hypothesis is based on the idea that tension along white matter axons causes the outward and inward folding of the cortex, in a manner to reduce or minimize this tension [56]. However, experimental evidence has not been supportive of this

hypothesis. For example, work in the ferret has shown that while axons are indeed under considerable tension in the developing brain, this tension tends to occur mostly in the subcortical white matter, located too deep to affect surface folding [58].

Another line of work, based on experimental manipulation of the developing cortex in fetal monkeys, demonstrates the importance of neuronal input for the development of the cortical sulco-gyral pattern [11,17,18]. In these experiments, surgical removal of part of the cortex results in abnormalities in the sulco-gyral pattern in cortical areas distant from the operation site, possibly due to lack of axonal input that would normally be incoming from the removed cortex. It is important to note that these changes in cortical folding cannot simply be explained by changes in axonal tension forces in the brain. More complex factors including axonal competition for synaptic space and circuit reorganisation are likely at play [17,18]. Regardless of the specific mechanism, however, there is powerful experimental evidence to suggest that the development of cortical folding patterns and the development of axonal connections are inter-related. The sequence and timing of these developmental events also supports this view. When neuronal migration has completed, the cortical surface is still essentially smooth [18]. It is only after neurons reach their final position in the cortex that axons begin to proliferate at a large scale in the brain, and this also when sulci and gyri begin to appear. Thus, the normal development of cortical folding cannot be explained only in terms of spatial distribution of neurons, it also depends on their axonal connections [18].

Thus, it is conceivable that prenatal abnormalities in these processes may be reflected in changes in the normal geometrical relationship between gray and white matter, as observed in our work. A recent review of genetic mutations in autism implicates these mutations in a variety of molecular mechanisms that interestingly appear to all converge on a few specific steps of neurodevelopment, namely axonal and dendrite outgrowth, and experience-based synapse modification [39].

Synapse modification is one of the most important processes in postnatal neurodevelopment. It has been shown that the normal human brain at birth is characterized by an extensive overproduction of axons, dendrites and synapses, which reaches a peak around age 1 [23]. In monkeys for example, [29] showed that the number of axons in the corpus callosum of newborns exceeds the number present in adults by at least 3.5 times. This type of overproduction is thought to impart plasticity to the newborn brain. In humans, after age 1, there is a prolonged period of reorganisational events, such as axon and synapse pruning, and naturally occurring neuronal death. These events are at their fastest from about age 5 through adolescence. The initial overproduction of neural structures followed by the removal of redundant synapses, axons and the reorganization of connections is thought to subside the development of advanced cortical organisation, which underlie the cognitive abilities of the human brain (e.g. [27,30,41]).

In addition to removal of excessive connections, the maturing brain is characterized by an increase of overall white matter volume [45], due to increased myelination of axons, as well as an expansion of cortical surface area, up to 4 times from infancy to adulthood [22]. All this knowledge may be the basis for a possible (speculative) explanation of the increase of

geometric coupling between gray and white matter in typically developing children from ages 6 to 14, as seen in our results.

This explanation would entail that at an early age the *pars orbitalis* area may have an initial overabundance of connections to various other areas, many of which may be pruned during childhood and adolescence. As a result of selective pruning, the interhemispheric connection with the contralateral *pars orbitalis* may gain “prominence” over other, less functionally important connections. This effect, together with the concurrent myelination (and repacking) of white matter fibers and the expansion of cortical surface area may result in a more “efficient” geometrical arrangement of white matter fibers relative to cortical geometry. These processes may in turn underlie the increase of the mutual information measure seen in our results with typically developing children.

Children with ASD, on the other hand, do not appear to show the same evolution over time. Our results show a higher mutual information value for children with ASD around age 6. This high “baseline” value may be a result of various neurodevelopmental abnormalities as discussed previously, and it does not appear to change with age. As mentioned earlier, this finding can be viewed in the context of numerous evidence that characterizes autism by an initial period of an overall brain overgrowth, from 0 to 4 years, followed by a premature arrest of growth [7]. For example, postmortem examinations in children aged 2 to 16 years revealed that there is 67% more neurons in the prefrontal cortex of children with autism than in their age matched controls [8]. It is thus possible that normal mechanisms of pruning and reorganisation during childhood and adolescence are altered and/or delayed in autism, and the lack of change in mutual information may parallel such disruptions in the normal maturation of the brain.

8 Summary and Future Directions

To summarize, our findings appear to support the possibility of an increased recruitment of the right hemisphere in ASD that develops before the age of 3 years, and they appear to support the view that ASD is characterized by a period of an early abnormal overgrowth, followed by a premature arrest of growth. We put our results in the context of various other functional and structural studies of the developing brain, in order to provide a broader background for our findings. Future work will aim at integrating our methodology with functional studies in order to address some of the hypotheses raised during the discussion.

Future work needs to be carried out also in order to address certain methodological aspects of this work. For example, the white matter geometry computation method introduced here includes a spatial scale parameter which is currently set to an empirically chosen value. In the future, we will develop an automatic scale selection method, which will allow the optimal scale value to be chosen at each point along the tract. This is expected to achieve an improved geometrical characterization. In addition, other surface geometry features need to be tested, for example the surface’s shape index, or curvedness [26]. Furthermore, the strength or nature of the relationship between white matter and gray matter geometry features could be measured by functions other than Mutual Information, for example kernel-

based methods [20]. Methods based on machine learning can also be applied to ‘learn’ the relationship between the two types of geometry.

The present experimental work focused on a single cortical region, the *pars orbitalis*. In future work, we will perform an investigation over a parcellation of the entire cerebral cortex, which will then be incorporated into a network analysis framework in order to detect global patterns of change. Finally, we will also develop the application of our methods to longitudinal studies. Our methods will serve to characterize normal patterns of brain structure development over time, and will help in detecting developmental abnormalities. In this manner, they can potentially be useful in performing early diagnosis of brain disorders.

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Fig. 1.
The orthonormal Frenet frame at a point along a helical curve segment (black), with the tangent vector E_T (red), the normal vector E_N (green) and the bi-normal vector E_B (blue).

Fig. 2.

Left: Our method computes at each point $\mathbf{p}$ a function on the unit circle orthogonal to the tangent vector E_T at $\mathbf{p}$ which measures the rate of change of E_T in all of these directions, thus computing a 2D “dispersion distribution function” (DDF). Right: To compute $\nabla_{\mathbf{v}} E_T$ at location $\mathbf{p}$ at scale S , we define a disk-shaped neighborhood with radius S around $\mathbf{p}$, over which vector field $F = \mathcal{U} E_T$ is averaged. The same averaging is performed over a neighborhood centered at $\mathbf{p} + S\mathbf{v}$ (orange). $\nabla_{\mathbf{v}} E_T$ is then approximated as the angular difference between the two vectors thus obtained.

Fig. 3.

The total dispersion (TD) visualized for tracts forming part of the corpus callosum, overlaid on a slice through the FA volume. Here and in subsequent figures, we use the rainbow colormap to render TD values on the tracts. Please keep in mind that fiber dispersion is a 3D phenomenon.

Fig. 4.

A fiber tract connecting the substantia nigra in the brain stem to the caudate nucleus (light gray-blue surface). The tract is overlaid on a slice through the T1 volume. The tract is colored by TD, for a range of values for scale parameter S .

Fig. 5.

A schematic illustration of the four steps in our pipeline. We first define the tract of interest with tractography (step 1), then we compute the geometry feature of interest of this tract, such as the dispersion distribution function (DDF, step 2). After extraction of the cortical geometry features of interest (step 3), we combine the geometry of the gray and white matter via Mutual Information (step 4).

Fig. 6. An anterior coronal view of the right hemisphere with fibers connecting the *pars orbitalis*. As in the previous figures, fibers here are colored by TD. Left: a volume rendering of the mean curvature of the GM/WM boundary surface, with blue/purple intensities denoting curvature sign and magnitude. Right: the T1 image, shown for anatomical reference.

Fig. 7.

Left: The set of tracts used in our group study shown for one subject. The fibers are colored by TD (computed at scale $S=10\text{mm}$), and are overlaid on an axial slice through the T1 volume registered to DWI space. Right: The same fiber tract shown with both a sagittal and an axial slice through T1.

Fig. 8.

Correlation in the Right hemisphere between Age (x-axis) and $M \equiv MI(TD, MC)$. Left: Control subjects (HC). Right: ASD subjects. Blue line: robust fit for the HC population. Red line: robust fit for ASD population. These findings are in agreement with the ASD model of [7], which argues that ASD is characterized by early brain overgrowth (age 0 to 4), followed by a delayed or arrested growth.