Published in final edited form as:

Multimodal Brain Image Anal (2012). 2012 ; 7509: 29–40. doi:10.1007/978-3-642-33530-3_3.

Genetics of Path Lengths in Brain Connectivity Networks: HARDI-Based Maps in 457 Adults

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Abstract

Brain connectivity analyses are increasingly popular for investigating organization. Many connectivity measures including path lengths are generally defined as the number of nodes traversed to connect a node in a graph to the others. Despite its name, path length is purely topological, and does not take into account the physical length of the connections. The distance of the trajectory may also be highly relevant, but is typically overlooked in connectivity analyses. Here we combined genotyping, anatomical MRI and HARDI to understand how our genes influence the cortical connections, using whole-brain tractography. We defined a new measure, based on Dijkstra's algorithm, to compute path lengths for tracts connecting pairs of cortical regions. We compiled these measures into matrices where elements represent the physical distance traveled along tracts. We then analyzed a large cohort of healthy twins and show that our path length measure is reliable, heritable, and influenced even in young adults by the Alzheimer's risk gene, *CLU*.

Keywords

Structural connectivity; neuroimaging genetics; Dijkstra's algorithm; HARDI tractography; path length

1 Introduction

Understanding the structural and functional connectivity of the brain's neural networks is critical for determining pathways and mechanisms underlying behavior and brain disease. Diffusion tensor imaging, and its mathematical extensions such as HARDI or *q*-space imaging, have been used to study anatomical connectivity in development [1] and in disorders such as Alzheimer's disease [2]. Such studies shed light on how connections and pathways are disrupted or altered in various diseases.

Analyses of neural network connectivity are increasingly popular, with a rapid rise in the use of methods to map functional and structural networks in the living brain. With diffusion

imaging and tractography, physical connections from one region of the brain to another can be tracked. By tracking pairwise connections between a set of N regions of interest on the cortex, we can summarize properties of these connections in a matrix. Graphs can be created, in which the nodes represent cortical regions, and edges represent the connections between them. Standard graph theory measures can often be used to summarize global properties of the network. For example, the ‘characteristic path length’ measures the average number of nodes that must be traversed to connect any one node in the graph to all the others. Despite its name, this average path length depends only on the network topology and not on how it is embedded in space: it ignores the length of any physical connection between the nodes (such as axons in the brain). When used for brain network analysis, the physical distance between cortical regions may also be relevant, as (among other factors) it may affect how vulnerable the connection is to lesions such as stroke, tumors, trauma, or degenerative processes.

In this work, we use tractography based on both high angular resolution diffusion imaging (HARDI) and co-registered standard anatomical MRI to map fibers in the brain connecting various cortical regions. We created maps of the proportions of fibers that interconnect various cortical regions within and across hemispheres and calculate an optimal path between cortical regions based on the fiber counts. By computing these connection matrices in a large cohort of 457 healthy adult twins, we were able to apply quantitative genetic analysis to discover how strongly our genetic make-up affects the lengths of paths connecting different cortical regions. In addition, regardless of the statistical analysis, the measures representing the length of the trajectory of fibers from one cortical region to another could also be used to weight an overall, topological measure of characteristic path length and determine the average length of fiber trajectory. We note that in network analyses, the metric embedding and spatial configuration of the brain’s network nodes is typically overlooked, but that same information may be of interest in trying to discover factors that affect the brain’s wiring efficiency.

Combining diffusion imaging with genetic analysis is also fruitful, and very recently several common genetic variants have been discovered that affect the integrity of the brain’s white matter [3–6]. In general, genetic studies begin by estimating the overall degree of genetic influence on brain measures, as a helpful precursor to candidate gene studies or genome-wide scans (GWAS) to identify factors that may influence white matter fiber connectivity [7]. Any genetically influenced connections or network properties could be prioritized as endophenotypes in the quest to discover specific genetic variants involved in the formation, insufficiency, and degeneration of these pathways. Twin studies have long been used to determine the degree of genetic influence over human traits. Monozygotic twins (MZ) share all their genes while dizygotic twins (DZ) share, on average, half. Here we used Falconer’s heritability statistic (h^2) to study how strongly DTI measures are influenced by our genetic make-up. Falconer’s heritability estimate is a simple measure that examines differences in intra-class correlations between the two kinds of twins, identical (MZ) and fraternal (DZ). If MZ twins are more highly correlated than DZ twins, we can infer that the trait is affected to some extent by genetic influences, and the proportion of variance due to genetics can also be estimated.

In this study, we use ODF-based tractography on state-of-the-art 4-Tesla HARDI images from 457 young adult subjects to define the first geometric measure of white matter path length underlying cortical connectivity. The resulting measure is heritable, and a topological analysis of the matrix reveals a genetic association to the Alzheimer's risk gene, CLU.

2 Methods

2.1 Image Acquisition and Subject Information

Whole-brain 3D anatomical MRI and HARDI scans were acquired from 457 genotyped subjects with a high magnetic field (4T) Bruker Medspec MRI scanner. T1-weighted images were acquired with an inversion recovery rapid gradient echo sequence. Acquisition parameters were: TI/TR/TE= 700/1500/3.35 ms; flip angle=8 degrees; slice thickness = 0.9mm, with a 256×256 acquisition matrix. Diffusion-weighted images (DWI) were acquired using single-shot echo planar imaging with a twice-refocused spin echo sequence to reduce eddy-current induced distortions. Imaging parameters were: 23 cm FOV, TR/TE 6090/91.7 ms, with a 128×128 acquisition matrix. Each 3D volume consisted of 55 2-mm thick axial slices with no gap and 1.79×1.79 mm² in-plane resolution. 105 images were acquired per subject: 11 with no diffusion sensitization (i.e., b_0 images) and 94 DWI ($b=1159$ s/mm²) with gradient directions evenly distributed on the hemisphere. Scan time was 14.2 minutes. In total, images from 457 right-handed young adults (mean age: 23.4 years, s.d. 2.0) were included, comprising 124 MZ (62 pairs) and 94 same-sex DZ twins (47 pairs), other subjects included different sex DZ twins, and siblings. Originally 545 scans were analyzed, but after rigorous quality control (removing images with artifacts or poor segmentation), 457 genotyped individuals remained.

2.2 Cortical Extraction and HARDI Tractography

Non-brain regions were automatically removed from each T1-weighted MRI scan, and from a T2-weighted image from the DWI set using the FSL tool "BET" (<http://fsl.fmrib.ox.ac.uk/fsl/>). A trained neuroanatomical expert manually edited the T1-weighted scans to further refine the brain extraction. All T1-weighted images were linearly aligned using FSL (with 9 DOF) to a common space with 1mm isotropic voxels and a 220×220×220 voxel matrix. DWI were corrected for eddy current distortions using the FSL tools (<http://fsl.fmrib.ox.ac.uk/fsl/>). For each subject, the 11 images with no diffusion sensitization were averaged, linearly aligned and resampled to a downsampled version of their T1 image (110×110×110, 2×2×2mm). b_0 maps were elastically registered to the T1 scan to compensate for susceptibility artifacts.

The transformation matrix from the linear alignment of the mean b_0 image to the T1-weighted volume was applied to each of the 94 gradient directions to properly reorient the orientation distribution functions (ODFs). We performed HARDI specific tractography as performed in [8] on the linearly aligned sets of DWI volumes.

Elastic deformations obtained from the EPI distortion correction, mapping the average b_0 image to the T1-weighted image, were then applied to the tract's 3D coordinates for accurate

alignment of the anatomy. Each subject's dataset contained 5000–10,000 useable fibers (3D curves) in total.

34 cortical labels per hemisphere, as listed in the Desikan-Killiany atlas [9], were automatically extracted from all aligned T1-weighted structural MRI scans using FreeSurfer (<http://surfer.nmr.mgh.harvard.edu/>) [10]. Labels were numbered 1–35, with no label segmented for region 4. The resulting T1-weighted images and cortical models were aligned to the original T1 input image space and down-sampled using nearest neighbor interpolation (to avoid intermixing of labels) to the space of the DWIs. To ensure tracts would intersect labeled cortical regions, labels were dilated with an isotropic box kernel of width 5 voxels.

2.3 Calculating the Connectivity Matrix and Fiber Density Maps

For each subject, a full 68×68 structural connectivity matrix was created. Each element described the proportion of the total number of detected fibers in the brain connecting each of the labels; diagonal elements of this matrix describe the total number of fibers passing through a certain cortical region of interest. In what follows, we will use the term *fibers* to designate the 3D streamlines or curves that result from whole brain tractography, even though strictly speaking only *post mortem* validation would reveal whether they correspond to true axonal pathways in the brain. If more than 5% of subjects had no detected fibers connecting the regions denoted by a matrix element, then the connection was considered invalid, or insufficiently consistent in its incidence in the population, and was not included in the analysis. For each connection across two nodes that was considered valid across the full healthy population (200 different connections from the full matrix were present in 95% of the population), a fiber density image was created. This image consists of a voxelwise mapping of the fibers intersecting the two regions, where a count of fibers crossing each voxel was made.

2.4 Path Length Calculations

Level sets and fast marching methods have been previously described to map structural brain connectivity by following the principal directional of diffusion anisotropy in DTI scans [11, 12]; even maps of connectivity defined in this way have been shown to be genetically influenced [13]. However, here, instead of the using the tensor information to propagate the flow of fibers, we use a map of fiber density, or counts of fibers at each voxel as a result of tractography, to map a path between one cortical region to another by following the trajectory of high fiber counts through discrete voxels. We note that this path may correspond, to some extent, with the path of information flow between cortical regions, as impulses are propagated along the axons recovered by tractography. We used Dijkstra's algorithm [14] to trace the path of highest density. Dijkstra's algorithm is a graph search method to find the shortest discrete path from a source node to every other node while minimizing the weight of the edges; it has been previously applied for tractography [15]. Here we focus not on following specific voxelwise paths in which fibers follow for tractography, but focus on the density of fibers at each voxel, following the path of highest density. In essence, this can help trace the most likely path of information flow from one cortical region to another.

All voxels in each person's 3D fiber density map were then considered as nodes in a graph; and each node in the graph is considered to be connected to 26 nodes (3D neighboring voxels) by undirected edges. Note that now we are considering adjacency in the 3D image, not the 2D matrix of cortical connections. Each edge was weighted inversely by the sum of the fiber densities at each of the two voxels on the edge, and the weight was inversely proportional to the Euclidean distance from the center of one voxel to the other. As the edge weights correspond to edge *costs* for our shortest path detection method, a connection between a pair of voxels that each had a high fiber density was assigned to a lower weight, or lower cost. Suppose voxels i and j are voxelwise neighbors with integer fiber counts

(densities) d_i and d_j respectively. Then we defined the edge weight as $W_{i,j} = \frac{1}{d_i + d_j}$. As most voxels in the density image are not immediate neighbors of each other (the region is generally an elongated path several voxels wide), the path graph can be represented by a sparse matrix. Dijkstra's algorithm would then follow the path of minimal edge weights, or maximal density connections.

To find the shortest path through the graph from one cortical connection to another, Dijkstra's algorithm requires the graph to have specified start and end nodes. A single point was selected at each region to serve as path start and end points to map the trajectory of the path from one cortical region to another.

A single representative point was calculated from each of the cortical regions of interest from the parcellated T1 image, and it was defined so as to avoid excessive influence of cortical folding patterns and depth on the position of the selected representative point. The representative point was selected based on all voxels from the entire segmented label (before label dilation). Voxel coordinates were transformed to spherical coordinates (r , radius, θ polar angle, and ϕ azimuthal angle) from the stereotaxic image center. The median radial distance from the center point was chosen to represent the depth along the surface. Only unique pairs of angles were retained to prevent over representation of inner and outer cortical points with the same angular projection. A 2D illustration of this is shown in Fig 1. Retained points were then converted back to the Cartesian space and the corresponding geometric mean was used as the center point. These points then served as the corresponding end points for each ROI. They were defined in such a way as to be less influenced by cortical folding patterns than the centroid of the regions.

Mapping the path from ROI-1 to ROI-2 would not necessarily follow the same path as that from ROI-2 to ROI-1. To ensure symmetry, we select the point with the highest fiber density in the pathway connecting the two regions of interest as the starting point. To make sure that the fibers in the pathway were in fact only those that intersected 2 ROIs, a fiber density map was created for each of 200 pairs of connections, by filtering the tractography output files. The point of maximal fiber density in only those fibers was chosen as the *start point*. If more than one point had the equivalent maximal density, the point with the minimal Euclidean distance from the midpoint of the two ROI endpoints was chosen as the start.

The algorithm will be incapable of finding an accurate connection between the two nodes if the graph structure is such that there are no edges from the subgraph containing the start

node with the subgraph containing the end node. As the fibers discretized into voxels, it is possible that the density image would not show a continuous path, but piecewise sections of fibers instead, as shown in 2D in Figure 1. To account for this possibility, and to avoid having tracts that do not start and end in different cortical regions, a 3D box was created spanning from the start point in one cortical region to the end point in the other. After the start and end points have been computed, this box is then artificially labeled with a uniform fractional fiber density count (0.5) to allow for a continuous path between different cortical regions to be connected, albeit at a high cost. Additionally, all voxels of the path were dilated (and given the small density count). This helps to ensure a continuous path such that the algorithm can find a set of voxel locations where it can create a representative path connecting the start and end regions.

Once the optimal path has been calculated based on the weights, the length of the path is computed by summing the distances from the center of the neighboring voxel points along the path, starting from the start point, following the path, and ending at the end point in the other cortical region. Alternative approaches might use tensor-derived measures such as FA as weights for each voxel visited along the path, or other scalar diffusion measures to describe the properties of the path.

Once all the path lengths have been calculated from all valid cortical connections to the next, an *observed path length* connectivity matrix can be computed. Instead of using each element to represent the proportion of fibers in the brain that run between the regions, the physical length of fibers connecting the regions is approximated. Dijkstra's algorithm was implemented in Matlab using <http://www.mathworks.com/matlabcentral/fileexchange/10922-matlabgl> the 'matlab_bgl' toolbox.

2.5 Overall Physical Path Length

In this study, brain network matrices were created by calculating a true path length between individual cortical regions. We used a single point determined from each of the segmented regions of interest, on the cortical surface, as an end point in a path. The distance along this path is calculated. The common topological measure *characteristic path length* (CPL) is an average measure (across the whole network) of the minimum number of edges necessary to travel from one node to another in the network (i.e., average minimum path length). To coincide with this common measure generally calculated using networks with matrix elements based on cortical activation correlations or proportions of fibers, we also calculated this overall path length index, using a weighting based on our 'physical path length'. This was performed using the Brain Connectivity Toolbox in Matlab [16].

2.6 Heritability of Path Length Analysis

In this study, we focused our analysis on the set of 'valid' connections. These are the detected connections that proceed from one brain region to another in almost all individuals in our sample. One goal of our work is to determine genetic influences on the brain, so we tested whether the path length connecting cortical regions across the corpus callosum is heritable. In genetics, the 'heritability' is the proportion of the observed variance in a measure that is attributable to genetic differences across individuals. To assess heritability, we use the fact

that our large sample consists of both monozygotic (MZ) and dizygotic (DZ) twins. If path length is in fact heritable, then the observed correlations among MZ twins should be higher than those between pairs of DZ twins, as MZ twins share all their genes while DZ twins share on average only half. If genes had no effect on the measures, then the correlations should not be any higher for MZ than DZ twins [17]. We computed intra-class correlations (ICC) within MZ and DZ twins, r_{MZ} and r_{DZ} respectively, to compute a simple measure of genetic effects: Falconer's heritability estimate, $h^2 = 2(r_{MZ} - r_{DZ})$ [18] at each subsequent connection (Falconer's h^2 is a simple but widely-used statistic; more complex structural equation models may also be used to estimate heritability). Here the ICC was calculated as

$$ICC = \frac{MSB - MSE}{MSB + MSE}, MSB = 2 \sum_{i=1}^N \frac{(\mu_i - \bar{\mu})^2}{N - 1}, MSE = \sum_{i=1}^N \frac{\sigma_i}{N}, \sigma_i = (N1_i - \mu_i)^2 + (N2_i - \mu_i)^2, \mu_i = \frac{N1_i + N2_i}{2}$$

where MSB corresponds to the mean square error between pairs; MSE is the mean squared error across the full set of pairs. N refers to the total number of pairs, while $N1_i$ and $N2_i$ represent each individual within pair i .

Reproducibility and reliability of the connections were assessed by examining the ICC for 12 unrelated subjects scanned twice with the exact same protocol, approximately 3 months apart. Tractography and cortical surface extractions were performed for both time points. For the reproducibility analysis, only unrelated subjects were analyzed because the inclusion of related subjects (e.g., MZ twins) could bias the estimate of reliability by reducing the MSE relative to what would be obtained by independent sampling of the young adult population.

2.7 Genetic Association of Overall Path Length

In this analysis, we found that our topological measure was quite heritable (see *Results*). To further delve into the possible genetic basis for the heritability, we also assessed effects of a candidate gene that was previously found to influence fractional anisotropy on DTI. The *CLU* single nucleotide polymorphism, at rs11136000, is a very commonly carried variant in the genome that is consistently associated with Alzheimer's disease in vast samples of tens of thousands of subjects [19] in recent work, it has also been shown to alter brain structure in healthy adults without AD [20]. The number of risk alleles a person carries (0, 1 or 2) at the rs11136000 locus was regressed against the overall 'characteristic' path length measure, as weighted by the approximate distance traveled as calculated above. As our subjects were related, we used a statistical mixed model, including a kinship matrix, to test associations [21]. We also covaried for the effects of age, sex, and brain size, which can clearly affect our measured lengths.

3 Results

Our path length matrices showed moderate levels of heritability (in 228 twins) and reliability (in 12 unrelated individuals scanned twice with a three month interval with both sMRI and HARDI), with reliability comparable to that observed for fiber count matrices in [22].

The standard topological measure, *characteristic path length*, was calculated (1) using matrices weighted by the distance between cortical regions as defined in this paper, and also (2) with the more standard “fiber count measure” where matrix elements represent the proportion of traced fibers connecting one region to another [23]. We find the heritability (as measured by Falconer’s h^2) of our new more accurately termed characteristic path length measure was 0.76, while for the more traditional measure, it was 0.08. This is promising for genetic studies; even though a high heritability – meaning strong genetic control – is not a guarantee that SNP effects will be large, it is certainly true that SNP effects are unlikely to be found at all for measures whose heritability is very low. For that reason alone, this new measure becomes a strong candidate for very large scale genetic association studies, such as those conducted by the ENIGMA consortium [7].

Such high heritability suggests the value of conducting a search for specific genetic influences on these pathways. We reserve an unguided search of the genome for future analysis, and use a candidate gene to show the potential of our measure here. As the *CLU* SNP has been previously shown to be associated with differences in white matter microstructure in healthy adults, here we tested whether it also was related to the global length of fiber paths traveled around the brain, based on the connection distances defined in this paper. We found that in fact a person’s *CLU* genotype was indeed associated with our global path length measure. Each additional copy of the AD-risk *CLU-C* allele was associated with a 0.9 voxel (1.8mm) increase in characteristic path length ($p=0.003$). This can perhaps reveal more mechanistic detail on the effect of the gene, perhaps even suggesting a less efficient brain network in people who carry the adverse variant of this risk gene.

4 Discussion

Here we developed a novel method to probe the genetic basis of anatomical brain connectivity. Rather than use network measures that depend only on the network topology and not on the path lengths, we used fiber density maps derived from HARDI tractography as a way to weight the edges or connections from voxel to voxel and estimate optimal path trajectories and lengths. We used this to define a new symmetric connectivity matrix based on this observed path length.

Our analysis of this large cohort of young adults allowed us to estimate heritability of structural brain network measures. In conjunction with fiber density at these elements across the matrix, path length matrices may offer robust analyses of connections, offering additional detail on connection properties.

This work suggests several follow up studies. While we examined specific genetic influences on the overall path length, the most genetically influenced individual connections may also be promising targets to prioritize in the search for genes influencing brain integrity and risk for psychiatric disease. Connections under strong genetic control may serve as powerful endophenotypes to search for specific genetic variants influencing the human brain.

Acknowledgments

This study was supported by the National Institute of Child Health and Human Development (R01 HD050735), and the National Health and Medical Research Council (NHMRC 486682), Australia. Genotyping was supported by NHMRC (389875). Additional support for algorithm development was provided by NIH R01 grants EB008432, EB008281, and EB007813. GP is additionally supported by the UCLA I2-IDRE Research Informatics and Computational Data Development Grant. GZ is supported by an ARC Future Fellowship (FT0991634).

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Fig. 1.

To select the representative point for each ROI, the spherical coordinates of all label voxels were calculated from the 3D center of the image (yellow circle). The median radial distance was calculated from all points along the cortical label (red curve). Also if two points were only different in their radius (blue solid line and thick black dashed line), then their angular components were only counted once to not over influence the mean. Subsequently, the geometric mean of all these points, back in the Cartesian image space, was calculated as the representative point for the cortical region.

Fig. 2.

Discretization of a fiber into a set of voxels in the image (here in 2D, but the 3D case is tackled in the paper) may leave a piecewise path (*dark blue*) rather than a connected one. Voxels are dilated (*light blue*) to ensure a connected path exists.

Fig. 3.

A) Full brain tractography is performed using HARDI based tractography on high field, high resolution images; B) Automatic cortical parcellation in Freesurfer [10] is simultaneously conducted on the T1-weighted high field scans. Once DWI and T1 scans are registered together to account for susceptibility artifacts, tracts are filtered to include only those going through pairs of cortical regions to create 200 filtered fiber density images, one for each valid pair of connections. C) Fibers that remain going through the left rostral anterior cingulate and left medial orbital frontal cortices are shown in yellow for a single subject. Representative points for each cortical region are extracted; points shown in black across brain surface, points of interest show in red; the highest density point is selected from the filtered fiber density file (shown as a green sphere). To ensure symmetry, the point of highest density is traced to each one of the red endpoints of interest based Dijkstra's algorithm following the highest density path. The resulting path is shown in blue. This represents only one element in the 68×68 path length connectivity matrix as all combinations of connections are calculated in the same way.

Fig. 4. (A) Connectivity map of the path length estimates for reliability and (B) the heritability. Certain connections, including the connection of the right insula with the right inferior temporal lobe show both high levels of heritability (~ 0.6) as well as high reliability as measured in 12 individuals (~ 0.6).