Development of the Structural Connectome Between Ages 12 and 30: An N=439 DTI Study

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Background

The human brain changes profoundly throughout life, and cortical maturation continues well into adulthood [1]. Changes in cortical areas are accompanied by remodeling of the neural networks that connect them, but little is known about these changes. Only one study has used graph theory to study this in adolescence [2]. **Graph theory** assesses brain connectivity by treating the brain as a collection of nodes (regions) and edges (connections). A number of parameters exist to describe the relationship between these nodes and edges. Characteristic path length (**CPL**) is an average measure of the path length in a network. Lambda (**λ**) is CPL normalized to random networks of the same size and complexity. Mean clustering coefficient (**MCC**) is a measure of how many neighbors of a given node are also connected to each other. Gamma (**γ**) is MCC normalized to random networks. Global efficiency (**EGLOB**) the inverse of CPL; networks with lower CPL are more efficient than those with greater CPL. Small-worldness (**SW**) represents the balance between network differentiation and network integration. Modularity (**MOD**) is the degree to which a system can be subdivided into smaller networks [3]. Degree (**DG**) is the number of nodes a given node is connected to. Regional efficiency (**EREG**) is efficiency calculated on nodal neighborhoods.

Methods

Participants – 439 right-handed individuals (211 female/126 male adults, mean age=23.6, SD=2.19; 31 female/24 male 12 year olds, mean age=12.3, SD=0.18; and 25 female/22 male 16 year olds, mean age=16.2, SD=0.37)

Tractography – Tractography was performed as described in [4], resulting in 70x70 matrices of the fiber density (normalized for total number of fibers traced) between 35 cortical regions in the left and right hemispheres.

Graph theory metrics - We used the Brain Connectivity Toolbox (https://sites.google.com/a/brain-connectivity-toolbox.net/bct/Home, [3]) to calculate 7 standard global measures of connectivity: CPL, λ, MCC, γ, EGLOB, SW, and MOD. We also calculated 2 standard nodal measures of connectivity: DG and EREG. These were calculated for whole brain and left and right hemispheres separately. We calculated these over a range of sparsities (.2-.3, in .01 increments), and calculated the area under the curve of those 20 data points to generate an integrated score for each measure. This was done to generate more stable scores.

Age regression – Age effects were modeled in the following linear mixed effects models

$$BCT \sim A + \beta_{age}Age + \beta_{sex}Sex + \beta_{TBV}TBV + \beta_{age^2}Age^2 + \alpha \quad \text{(Eq. 1)}$$

$$BCT \sim A + \beta_{age}Age + \beta_{sex}Sex + \beta_{TBV}TBV + \alpha \quad \text{(Eq. 2)}$$

TBV = total brain volume, BCT = graph theory measures

Scan – 4T Bruker Medspec MRI. Anatomical (T1) parameters: inversion recovery rapid gradient echo sequence; TI/TR/TE=700/1500/3.35ms; flip angle=8 degrees; slice thickness=0.9mm, 256x256x256; HARDI parameters: single-shot echo planar imaging with twice-refocused spin echo sequence to reduce eddy current induced distortions; 23cm FOV, TR/TE=6090/91.7ms, 128x128; each 3D volume consisted of 55 2-mm thick axial slices with no gap and 1.79x.1.79 mm^2 in-plane resolution. 105 images per subject: 11 with no diffusion sensitization (T2-weighted b0 images) and 94 diffusion weighted (DW) images (b=1159 s/mm^2) with gradient directions evenly distributed on the hemisphere.

References

[1] Gogtay et al., Dynamic mapping of human cortical development during childhood through early adulthood. **PNAS** 101:8174-8179, 2004.

[2] Hagmann et al., White matter maturation reshapes structural connectivity in the late developing human brain. **PNAS** 107:19067-72, 2010.

[3] Rubinov & Sporns, Complex brain networks: graph theoretical analysis of structural and functional systems. **Nat Rev Neurosci** 10:186-198, 2009.

[4] Jahanshad et al., High angular resolution diffusion imaging (HARDI) tractography in 234 young adults reveals greater frontal lobe connectivity in women. **ISBI**, 2011, 1-5.

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Results

Results from all global analyses that passed significance are shown in the scatter plots in **Figure 1** and a summary picture is shown in **Figure 2**.

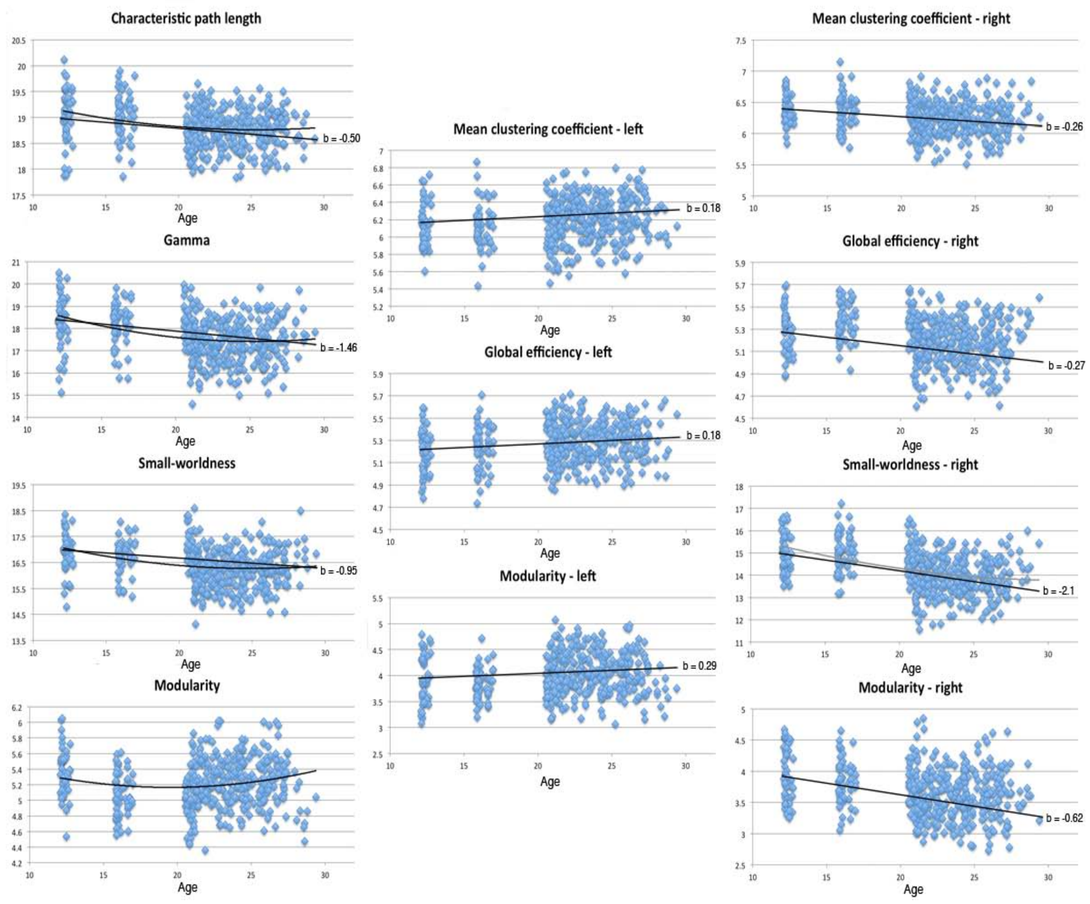
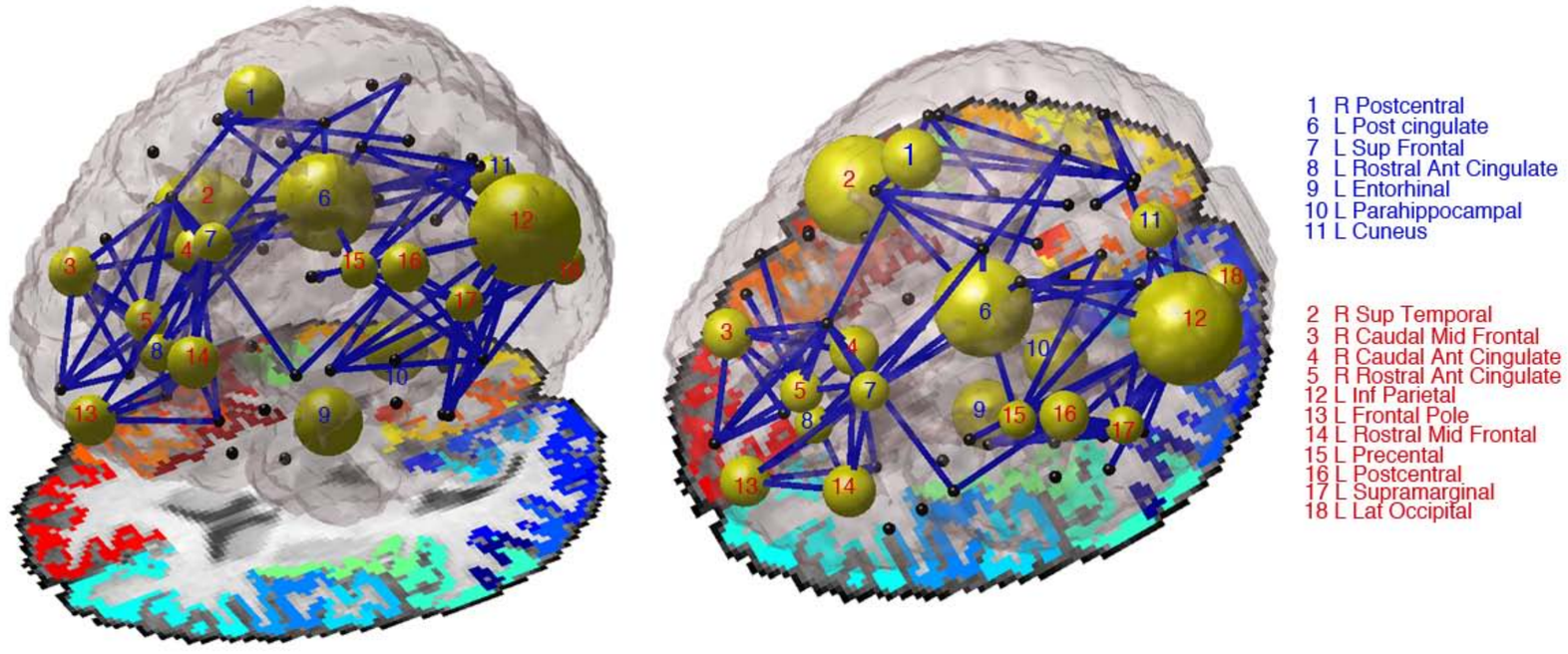


Figure 1. Scatterplots showing significant associations between global graph theory connectivity scores and *age* in whole brain, left, and right hemispheres. Linear trendlines added with slopes and *b* values.

Figure 2. Summary picture showing age effects on nodal degree and network connections. The diameter of each node is inversely proportional to the *p*-value for the degree analyses – large diameter means the node was significantly different in degree between children and adults. Non-significant nodes are colored black. Nodes numbered in blue increase in degree with age, while those numbered with red decrease in degree with age. Blue connections are those that changed with age (present in >95% of subjects).



Path length (and lambda), gamma, small-worldness, and modularity all decreased with age across the whole brain and in the right hemisphere. The left hemisphere showed opposite trends, however, with clustering, efficiency and modularity all increasing with age. Among nodal analyses we report only those with degree here. There were both increases and decreases in nodal degree and connection fiber density, scattered across various brain regions.

Discussion

We found a number of **linear and nonlinear age trends** in global and nodal graph theory measures of connectivity calculated for structural matrices derived from HARDI scans. Overall, the results point to a process of **increased network integration** across development – decreased CPL could be a result of non-essential connections being pruned to become more streamlined; MCC and γ are measures of network segregation, and they decrease; MOD is also a measure of network segregation, and it also decreases. The nodal increases and decreases in degree were scattered across the brain, but there were more **decreases in degree in the frontal cortex** than increases, and more **increases in degree in the temporal cortex** than decreases. This may be due to the different developmental trajectories of different brain regions.

The **different trajectories in left and right hemispheres** are curious, and possibly due to different developmental processes within each hemisphere, or it could be due to left/right asymmetry in volume.

Future work – we are increasing our N and adding an 18 year old cohort that will help fill a gap in our subject pool. Understanding the developmental trajectory for healthy subjects is the first step to understanding how these processes are affected in neurodevelopmental disorders.

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