Graph network measures of brain connectivity and its relation with behavior and cognitive performance in preterm-born 6 years-old children

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INTRODUCTION

Understanding the organization and variability of connectivity in normal brain development can offer insight into the developmental origin of childhood and adult brain disorders. Indeed, there is increasing interest towards assessing the development of white matter (WM) fibers underlying the complex brain connectivity [1], since the development of functional connections is clearly dependent on the establishment of cerebral fiber pathways [2,3], their maturation and myelination. In addition, correlation of structural connectivity with specific brain cognitive and behavioral brain functioning can define new quantitative and qualitative MRI biomarkers of brain organization and function especially during development. The goal of this work is to study the brain connectivity and network model based segregation of structural connectivity associated with cognitive and behavioral scores in prematurely born children. We used graph theory-based connectivity analysis and stepwise linear regression models to assess the contribution of brain connectivity as well as subjects covariates such as gestational age (GA) and birth weight (BW) in cognitive and behavioral performances of premature born children.

METHOD

We recruited 50 premature born children six years old, from the Child Developmental Unit at the University Hospitals of Geneva and Lausanne. Gestational age (GA) at birth ranged from 24 to 33 weeks and birth weight (BW) ranged from 510 g to 1150 g. All subjects were free from prematurity associated brain lesions and ventriculomegaly at term equivalent age and the 6 years-old scans were read as normal by experienced neuroradiologists. The scanning protocol included: T1-weighted MPRAGE (TR/TE=2500/2.91, TI=1100, resolution=1x1x1mm) and diffusion-sensitized EPI sequence (30 directions, max bvalue=1000 s/mm^2, TR/TE=10200/107, resolution=1.8x1.8x2 mm) on a Siemens 3T Tim Trio system. For each subject the connectivity matrix was computed using the Connectome Mapper Toolkit [4]. We model the structural brain networks as undirected weighted networks with the nodes being the centroid of each cortical (and subcortical) region of interest (ROI) and the edges the average connection density of all subjects weighted by the individual connection efficacy (i.e. the mean fractional anisotropy (FA)) along the bundle connecting the two ROIs) (see figure 1). Using the Brain Connectivity Toolbox [5], we computed 3 global (average shortest path length, global efficiency and transitivity), and 6 average nodal network measures: average node degree, efficiency, strength, clustering coefficient (clustering index), betweenness centrality and eccentricity. Cognitive assessment, at time of scan, was carried out in all subjects using the French version of the Kaufmann Assessment Battery for Children (K-ABC) [6]. Four types of behavior: emotional symptoms; hyperactivity/inattention; peer relationship problems; total difficulties score and prosocial behavior were assessed using the French version [7] of the Strengths and Difficulties Questionnaire (SDQ) [8]. Social reasoning abilities were assessed administering the experimental Social Resolution Task (SRT) [9]. A generalized linear model (GLM) with stepwise regression was computed to predict cognitive and behavioral performances in patients using the brain global and average nodal network measures, as well as gestational age (GA) and birth weight (BW). All analyses were performed with informed parental consent and were approved by the medical ethical board of both hospitals.

RESULTS

GLM analysis showed significant correlation between GA, BW and network measures with the cognitive and behavioral scores (see figure 2). BW, average node degree (deg) and clustering index (CI) was associated with SRT Q1 (adj-R^2 = 0.33,$p < 0.01$) and SRT Q2 scores (adj-R^2 = 0.18,$p < 0.01$). SDQ emotional score was influenced by GA, average shortest path length (lambda), average node strength (str), degree and eccentricity (ecc) (adj-R^2 = 0.16,$p < 0.05$), though showing a relatively small correlation coefficient. SDQ hyperactivity and inattention score show significant correlation (adj-R^2 = 0.16, $p < 0.001$), with GA, average shortest path, average node degree and transitivity (trans). Further average node degree, betweenness centrality (bet) together with patient covariates (GA, BW) allowed us to significantly predict SDQ prosocial score (adj-R^2 = 0.26,$p < 0.05$). GA, transitivity and average node efficiency was significantly associated with K-ABC composite scores (adj-R^2 = 0.17,$p < 0.01$) while K-ABC simultaneous scores show an adjusted R^2 of 0.35 when predicted by the average shortest path, average node eccentricity and clustering index ($p < 0.001$)

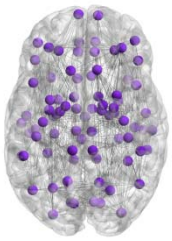

Figure 1: Graph model (axial view). Purple spheres, ROI centroids. Edges, FA-weigthed structural connectivity

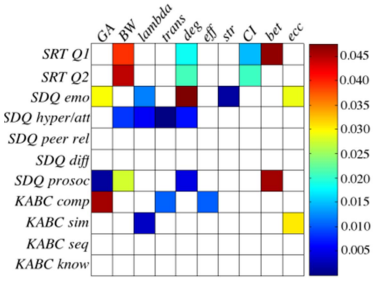

Figure 2: In each column, stepwise regression predictors. In each row, cognitive and behavioral scores. Colors code the p-value of each predictor in the regression of each

DISCUSSION and CONCLUSION

In the present study, we have applied connectome analysis techniques and graph model-based brain network measures in a group of prematurely born children in order to assess the influence of brain connectivity on cognitive performance and behavior. Our results confirm the well-known influences of BW and GA [10] on cognition and behavior. In addition, our main results show that social behavior tasks and hyperactivity were related to average node degree, transitivity and shortest path length. Further, shortest path length, transitivity and network efficiency predicted the variability in the cognitive performance in this population at high risk for structural and functional brain abnormalities.

In conclusion, the overall network measures show correlation with cognitive and behavioral skills that may explain long-term difficulties in learning and social behavior of these children. Next step will be the identification of hubs, or distributed subnetworks in order to further understand global brain integration and segregation in these children and its possible correlation with cognitive and behavioral scores, as well as explore correlations with local network measures.

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