Graph theory to analyse developmental plasticity in connectivity of preterm children

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INTRODUCTION

Diffusion MRI (dMRI), due to its unique ability to non-invasively visualize and quantify in vivo white matter tracts in the brain, can provide an insight in structural brain connectivity. Indeed, structural brain connectivity can be modeled as a graph [1,2,3]. This graph representation is used to represent pair wise relations between interregional ensembles of neuronal elements (nodes), where the links represent anatomical connections formed by white-matter axonal paths [4]. This structural connectivity by means of dMRI may shed new lights into understanding disease as it probes the microstructural aspects of the brain tissues. However, little is known about connectivity changes in brain development. Understanding rate and variability of connectivity in normal brain development, and detect differences from typical development offers insight into the developmental origin of childhood and adult brain disorders. Indeed, premature birth and intra uterine growth restriction (IUGR) are major risk factors for longterm morbidities, including developmental disabilities such as cerebral palsy, mental retardation and a wide spectrum of learning disabilities and behavior disorders in children. Recent studies suggest that early brain developmental alterations in extremely preterm infants (EP) and growth restricted preterm infants (IUGR) are associated with abnormal behavior and cognition in childhood [6,7,8]. To understand the neurostructural origin of these disabilities and to investigate the effect of EP and IUGR in pre-school children aged 6 years old we have used structural connectivity graphs derived from whole brain structural connectivity matrix (connectomes).

SUBJECTS

Sixty prematurely born children aged six years old, recruited from the Child Developmental Unit at the University Hospitals of Geneva and Lausanne underwent MRI examinations on a 3T Siemens TrioTim system [9]. T1-weighted MPRAGE images (TR/TE=2500/2.91, TI=1100, res.=1x1x1mm, 256x154) were acquired. Diffusion weighted images were acquired using a diffusion-sensitized EPI sequence providing whole brain coverage. Following an acquisition without diffusion sensitization, images were acquired with gradients (max. b-value= 1000 s/mm^2) applied in 30 directions (TR/TE=10200/107, res=1.8x1.8x2 mm). Birth weight (BW), gestation age (GA), and infant growth parameters were collected. All studies were performed with informed parental consent and were approved by the medical ethical board of both hospitals. 53 subjects were finally considered (7 data sets where discarded due to bad quality). Infants were classified in 3 groups: 21 were born moderately preterm with *Intra Uterine Growth Restriction (IUGR)* after placental insufficiency, 23 were born <28 week of gestation age (GA) and were classified as *Extreme Premature (EP)*. The *control group* comprised children born moderately preterm with normal birth weight (BW) (see right table).

Groups	Control	EP	IUGR
Count MRI	9	23	21
Gender repartition	3M / 6F	11M / 12F	12M / 9F
GA at birth	32.02 ± 2.47	26.34 ± 1.29	30.05 ± 3.07
Birth weight	1652.50 ± 402.45	943.26± 198.17	919.54 ± 328.28

METHOD

For each subject, the extraction of the connection density matrix was performed using an in-house software following the procedure developed by Hagmann et al. fully described elsewhere [10, 11] and freely available in [12]. To compute the individual connectomes, based on [1], we defined them as being composed of two components: *connection density* and *connection efficacy*. The *connection density component* was built as the average of all subjects' density matrix in a group (one single matrix for each group), as we assumed that the connection density maintains the same pattern inside a group. Then, for each subject, we defined the *efficacy component* as a subject-dependent matrix storing the mean fractional anisotropy (FA) value of the bundle connecting each pair of cortical regions. Thus, each individual participant contribution was considered to be the product of their own *connection efficacy component* (based on the FA and unique for each subject, like a fingerprint) and the *connection density component* of the group it belongs to (so that all individual connectomes within a group maintain an equal number of pathways). Individual graphs derived from the connectomes were then computed using the brain connectivity toolbox (freely available in [13]) and compared in terms of global network efficiency, minimum path length and transitivity as defined in [3,4,5]. Efficiency and path length are measures of network's integration, with efficiency measuring how efficiently the network exchanges information and path length being the network's average shortest path length. Transitivity (first proposed by Newman, Watts and Strogatz) is a global alternative to the clustering coefficient. Local clustering coefficient of a vertex in a graph quantifies how close its neighbors are to being a complete graph. Is the fraction of triangles around a node ('triplets'), in other words, the degree to which nodes in a graph tend to cluster together. Transitivity is defined as the ratio of 'triangles to triplets' in the network.

RESULTS

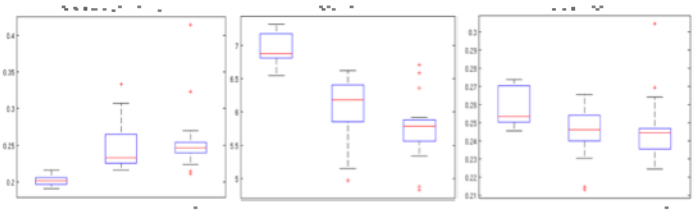

Figure 1: Boxplots for network measures' values for the 3 groups of subjects: average path length (1A), efficiency (1B) and transitivity (1C). In each plot: control subjects (left box), EP subjects (middle box) and IUGR subjects (right box).

As displayed in fig.1 extreme premature children (EP) and preterm infants born with an additional intra-uterine growth restriction (IUGR) both present a significant reduction in network efficiency (figure 1B) in concordance with a significant increase in average path length (figure 1A) (see table 1 for p-values). However, the variation in these network's integration measures appear higher in the case of preterm infants born with additional IUGR. The global network transitivity (fig. 1C), maintains the same pattern in both groups when compared with control subjects with only a slight decrease. However, this measure, even if smaller than control for both groups, appears lower for IUGR subjects (table 1).

Table 1: Network measures' mean values and p-values after ranksum tests.

Network measures	Control vs. EP comparison			Control vs. IUGR comparison		
	Mean values			Mean values		
	Control	EP	p-values	Control	IUGR	p-values
Average path length	0.2024	0.2465	$3.65\ 10^{-5}$ *	0.2024	0.2554	$6.98\ 10^{-5}$ *
Efficiency	6.94	6.07	$4.39\ 10^{-5}$ *	6.94	5.75	$6.98\ 10^{-5}$ *
Transitivity	0.2584	0.2453	0.032	0.2584	0.2457	0.0050 *

DISCUSSION

The goal of this work was to determine the effect of extreme prematurity and prenatal growth restriction on neurostructural outcome in pre-school children at age 6 year-old. We have used DTI and connectivity network analysis as it appears as a useful tool for exploring connectivity relationships between subjects groups. This more comprehensive map of brain connectivity enabled us to assess that, when compared to control subjects, both EP and IUGR subjects show a lower network efficiency (with an increase average path length), which might well contribute to learning disabilities and behavior disorders linked to pretem infants at school age. However, the network transitivity did not show the same statistical difference between the three groups, with only IUGR children showing a significant lower transitivity than controls. It may be due to the variability within the EP group, or a higher network clustering to overcome smaller efficiency in IUGR. We therefore suggest that extreme prematurity and prenatal growth restriction differently affects brain connectivity. The next step of this work will be to relate this results to local network measures to detect regions with structural connectivity differences in these groups of subjects, especially the node clustering coefficient. We might find a higher clustering coefficient in specific regions to overcome smaller efficiency, with some regions more affected than others, giving no influence in the global transitivity (global network clustering).

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