Brain network modular fingerprint of premature born children

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Introduction

The human brain network proved to be small-world and organized according to a hierarchical modular architecture, composed by communities of nodes highly interconnected between them, but sparsely connected with other modules [1]. This modular structure of brain networks is thought to be a crucial characteristic in terms of brain evolution and development [2]. Thus, characterizing brain communities fingerprints in normal brain development and finding alterations due to risk factors such as extreme prematurity and/or intrauterine growth restriction, can offer insight into the developmental origin of childhood and adult brain disorders. Here we characterize the modular topology of structural brain networks of children born extreme premature and/or with additional growth restrictions, and we quantify the similarity of their brain communities' structure using information theory derived metrics. In order to characterize the communities' fingerprint in such cases, we used the *consensus-clustering* algorithm [3] as a means to estimate a smooth representative group partition for each cohort. Though having small-world and hierarchical modular architecture, children born extreme premature and/or after IUGR show statistically significant different topology of their brain networks.

Methods

40 premature born children aged 6 years underwent MRI imaging on a 3T Siemens TrioTim, 32-channels coil. 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). 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. Infants were distributed in 4 groups: 10 were born <28 week of gestation age (GA) and classified as extreme premature (EP) ; 11 were born moderatelly preterm with intrauterine growth restriction after placental insufficiency (from now IO, *iugr-only*), 11 were born <28 week of gestation age (GA) with additional intrauterine growth restriction (IE, for *iugr+EP*). The control group (CTRL, n = 8) comprised children moderatelly preterm with normal birth weight (BW). For each subject the connectivity matrix was computed using the Connectome Mapper Toolkit (www.cmtk.org) [4] following the methodology described in [5]. 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. For each network, the optimal decomposition into modules was determined using the Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/) by selecting the highest modularity partition from 100 runs of the Louvain algorithm [6]. To quantify the inter-subjects' variability of the modular decomposition and the distance between individual subject's partition we used the random index (RI) and the normalized mutual information (MI) and the normalized variation of information (VI) values, as described in [7]. Finally, the representative brain network partition for each group was computed by means of the consensus-clustering algorithm (CC) [3].

Results

The 4 groups showed modular brain network architecture with similar coefficient of modularity and number of modules (see table 1). Within each group, RI, MI and VI indexes did not show any statistical significant difference, though for the 3 case groups we found a higher dispersion in these values. On the contrary, inter-group differences appear highly significant in all cases, with IO subject showing the highest significance (table 2). In the case-case comparison (i.e. EP vs. IO/IE and IO vs. IE) we found again highly significant differences between groups, though no significance was found in RI, MI, VI and when comparing subjects in the same group (table 3). The group representative brain network partitions in terms of CC for each group are shown in figure1.

Figure 1. Group CC representative partitions. Row-wise: (A) CTRL, (B) EP, (C) IO and (D) IE. Colors indicate brain modules with different color showing different modules with no other anatomical meaning.

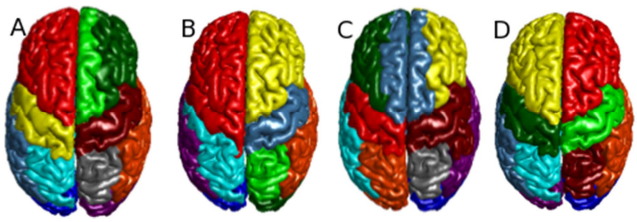

Table 1:mean number of modules and modularity index for all subjects within a group

	CTRL	EP	IO	IE
Mean number of modules	11	9	11	10
Mean modularity index	0.69	0.7	0.7	0.7

Table2 : p-values for case-control comparison

CTRL vs. EP	RI	MI	VI
Inter-group	1.45E-04	2.45E-07	7.08E-09
CTRL vs. IO			
Inter-group	4.06E-08	2.17E-06	4.76E-06
CTRL vs. IE			
Inter-group	0.009	4.10E-03	6.67E-04

Table 3: p-values for case-case comparison

EP vs. IO	RI	MI	VI
Inter-group	3.57E-22	1.03E-17	1.83E-15
EP vs. IE			
Inter-group	0.0014	1.00E-03	1.90E-03
IO vs. IE			
Inter-group	8.84E-12	4.69E-15	2.53E-16

Discussion

The goal of the study was to study the modular brain network structure in preterm born infants (with or without additional intrauterine growth restriction) and characterize their brain network communities' fingerprint. The decomposition of each individual brain networks in consistent modules enabled the comparison between groups using several measures of clustering similarity. As we can assume that one subject's partition is similar to another if the distance (in terms of RI, MI and/or VI) between each subject of the group is small and vice versa, the relatively highly significant differences found in both case-control and case-case comparisons talk in favor of a group-specific different modular brain network structure. Moreover, the visual inspection of the individual and representative consensus clustering (CC) partitions (fig.1 A), corroborate the analytical results, and allows us to hypothesize that IE subjects are "closer" in brain structure to EP subjects whilst IO subjects appear to have the most different structure with a higher number of modules in their group representative partition, with each of these partitions containing less network nodes.

Conclusion

We use brain network analysis and cluster decomposition to assess brain modular structure in children born prematurely and/or with additional prenatal growth restriction. Though all groups showed brain network modular and hierarchical structure (with equivalent number of modules and modularity index), a more in-depth analysis demonstrates that each cohort can be described by an own brain network modular architecture, such a fingerprint, paving the way to characterizing brain communities fingerprints to detect brain alterations.

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