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Brain network characterization of high-risk preterm-born school-age children

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ABSTRACT

Higher risk for long-term cognitive and behavioral impairments is one of the hallmarks of extreme prematurity (EP) and pregnancy-associated fetal adverse conditions such as intrauterine growth restriction (IUGR). While neurodevelopmental delay and abnormal brain function occur in the absence of overt brain lesions, these conditions have been recently associated with changes in microstructural brain development. Recent imaging studies indicate changes in brain connectivity, in particular involving the white matter fibers belonging to the cortico-basal ganglia-thalamic loop. Furthermore, EP and IUGR have been related to altered brain network architecture in childhood, with reduced network global capacity, global efficiency and average nodal strength. In this study, we used a connectome analysis to characterize the structural brain networks of these children, with a special focus on their topological organization. On one hand, we confirm the reduced averaged network node degree and strength due to EP and IUGR. On the other, the decomposition of the brain networks in an optimal set of clusters remained substantially different among groups, talking in favor of a different network community structure. However, and despite the different community structure, the brain networks of these high-risk school-age children maintained the typical small-world, rich-club and modularity characteristics in all cases. Thus, our results suggest that brain reorganizes after EP and IUGR, prioritizing a tight modular structure, to maintain the small-world, rich-club and modularity characteristics. By themselves, both extreme prematurity and IUGR bear a similar risk for neurocognitive and behavioral impairment, and the here defined modular network alterations confirm similar structural changes both by IUGR and EP at school age compared to control. Interestingly, the combination of both conditions (IUGR + EP) does not result in a worse outcome. In such cases, the alteration in network topology appears mainly driven by the effect of extreme prematurity, suggesting that these brain network alterations present at school age have their origin in a common critical period, both for intrauterine and extrauterine adverse conditions.

1. Introduction

It is now commonly accepted that risk factors such as early exposure to extra-uterine environment or antenatal adverse conditions such as intrauterine growth restriction (IUGR) affect the brain structure. Extreme prematurity (EP) and IUGR have both been associated with regional changes in brain structures such as the cerebellum (Limperpoulos et al., 2005) and with reductions in gray matter (GM) and white matter (WM) volumes, specifically in the thalamus, hippocampus, orbitofrontal lobe, posterior cingulate cortex, and centrum semiovale (Ball et al., 2012; Padilla et al., 2011; Lodygensky et al., 2008). Other studies report further diminutions in cortical gray matter volume (Inder and Hüppi, 1999; Borradori-Tolsa et al., 2004), as well as in cortical surface gyrification (Dubois et al., 2008), proving the high susceptibility of the human brain to the consequences of altered fetal environment and/or premature birth. Yet, the structural reorganization of the brain following premature birth is striking and illustrates the functional and structural plasticity of the developing brain (Kostović et al., 2014).

These brain changes in the neonatal period have been linked to altered neurodevelopmental outcome later in life (Kwon et al., 2014; Jaekel et al,. 2013; Ment et al., 2009). They have been associated with developmental disabilities such as cerebral palsy, mental retardation

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and a wide spectrum of learning disabilities and behavior disorders present in infancy and childhood (Ure et al., 2015; Ullman et al., 2015; Johnson S. and Marlow N., 2011 Woodward et al., 2006). Detailed neuropsychological studies prove that in adolescence, children born very preterm show executive function impairments in tasks involving response inhibition, visual-perceptual tasks and mental flexibility (Johnson et al., 2011). In children born preterm, WM abnormalities particularly in the frontal lobe have been associated with impaired neurocognitive function (Duerden et al., 2013). Interestingly, moderately preterm infants with IUGR show the same incidence of about 40% of cognitive deficits as EP children (Guellec et al., 2011), leading to a large societal burden of neurocognitive under-achievement.

In this context, and since the development of functional connections is clearly dependent on the establishment of cerebral fiber pathways, their maturation and myelination (Supekar et al., 2012; Smyser et al., 2010;), we hypothesized that the extremely preterm born children (<28 weeks gestation), and children born moderately preterm (28–37 weeks gestation) with IUGR will show different brain structural abnormalities depending on at what time in development the insult takes place, predisposing them to specific cognitive and behavioral deficits distinct from control preterm infants.

Diffusion MRI (dMRI) allows studying white matter tracts in-vivo and non-invasively by means of connectivity matrices (or connectomes) (Hagmann et al., 2012, 2008; Sporns and Zwi, 2004). A brain connectome can be seen as a network (equivalently, a graph), representing pairwise relations between interregional ensembles of neuronal elements (nodes), where the links represent anatomical connections formed by white-matter fiber paths (Meskadji et al., 2013; Sporns O., 2012; Bullmore and Basset, 2011). This abstract representation of a complex system such as the brain makes graph theory a suitable framework for mathematical analysis. Indeed, this network model allows looking at the brain as an integrative complex system, and enables quantifying rates of brain structural variability in terms of measures of network integration, segregation and topology (some basic notions on network measures are resumed in Boxes 1, 2 and 3).

Connectomics has been mainly used in adult populations in the study of a broad spectrum of brain disorders such as epilepsy (Lemkaddem et al., 2014), schizophrenia (Griffa et al., 2015) and mild cognitive impairment (MCI), among others (see Griffa et al., 2013 for a review). In pediatric populations, connectomics has been used to study brain development beginning at its early stages and continuing through adolescence and adulthood (Pannek et al., 2014; Dennis and Thompson, 2014; Kim et al., 2014; Tymofiyeva et al., 2013; Hagmann et al., 2012; Fan et al., 2011). From this point of view, the human brain network can be considered to be a small-world network that is organized according to a hierarchical modular architecture, composed by communities of nodes highly interconnected between them, but sparsely connected with other modules (Bullmore and Sporns, 2009). This modular structure of brain networks is thought to be a crucial characteristic in terms of brain evolution and development (Meunier et al., 2009).

Prenatal (neuro)development is a highly dynamic process, with an initial phase of abundant formation of new connections, followed by a phase of selection and pruning of connections (Innocenti and Price, 2005). The major axonal projections are formed mainly between mid-gestation and term birth, leading to the establishment of all major macroscopic white matter tracts as early as birth. A recent global brain network study demonstrates that even early in development, human brain already exhibits an adult-like structural network organization, showing both small-world characteristics (Ratnarajah et al., 2013) and rich-club organization (Ball et al., 2012). Indeed, it has been shown that full-term

Box 1
| Network integration

Ability to rapidly combine specialized information from distributed brain regions.
Path length: number of steps required for moving from a given node to another. Generally, only the shortest path is considered, i.e. the average shortest distance between any two nodes.
Global efficiency: quantifies the exchange of information across the whole network where information is concurrently exchanged.
Node degree: represents the number of connections of a given node.
Node eccentricity: *the greatest (geodesic) distance between this node at any other node in the network. It can be thought of as how far a node is from the node most distant from it in the graph*.

Box 2
| Network segregation

Ability for specialized processing to occur within densely interconnected groups of brain regions. Measures of segregation are related with clustering around individual nodes.
Local efficiency: quantifies a network's resistance to failure on a small scale. That is, the local efficiency of a node characterizes how well its neighbors exchange information when it is removed.
Clustering coefficient: Quantifies the number of connections that exist between the nearest neighbors of a node as a proportion of the maximum number of possible connections. It reflects presence of highly interconnected groups of nodes.
Betweenness centrality: is an indicator of a node's centrality in the network. It is equal to the number of shortest paths from all vertices to all other that pass through that node. A node with high betweenness centrality has a large influence on the transfer of items through the network.

Box 3
| Network topology

Arrangement of the various elements of a network (links, nodes, etc). Human brains are characterized by 'small-world' network topology that combines high levels of local clustering among nodes and short paths linking nodes of a network.
Hubs: nodes with high degree. They are seen as central nodes that demonstrate a large proportion of shortest paths. This measure is closely related to the modularity of the network. Hubs can be described in terms of their roles in different network communities. Provincial hubs are connected mainly to nodes in their own modules, whereas connector hubs are connected to hub nodes in other modules.
Small-world network: characterized by the presence of abundant clustering of connections combined with short average distances between neuronal elements. In such networks, most nodes are not neighbors of one another, but can be reached from every other by a small number of hops or steps. These networks maximize information processing while minimizing wiring costs, support segregated and integrated information processing, and present resilience against pathology.
Modularity: measure of the structure of networks or graphs. Roughly, it quantifies the ease with which whole-brain network can be divided into distinct subnetworks or "modules" (also called groups, clusters or communities). Networks with high modularity have dense connections between nodes within modules but sparse connections between nodes in different modules.
Rich-club index: is a metric on networks designed to measure the extent to which well-connected nodes also connect to each others.