THE NEONATAL PRETERM BRAIN: A CONNECTOME ANALYSIS

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Synopsis

Prematurity disrupts brain maturation during a critical period of development, leading to structural brain alterations that might underlie the observed later neurodevelopmental impairments in preterm children. Using diffusion MRI based whole-brain constrained spherical deconvolution tractography, we constructed structural connectomes to study the impact of prematurity on neonatal brain network organization at term-equivalent age. We found that, globally, in comparison to full-term infants, structural networks of very-preterm infants at term showed an increased segregation and decreased capacity to integrate information across brain regions and, in particular, a diminished connectivity strength in subnetworks localized mainly in frontal, limbic and para-limbic regions.

INTRODUCTION

The third trimester of gestation is characterized by a rapid brain growth, neurogenesis[1-4] and the emergence of large-scale brain networks.[5-8] Preterm birth disrupts brain maturation during a critical period of brain development,[9,10] leading to brain structural alterations which might be at the origin of the later neurodevelopmental impairments observed in preterm infants.[11-18] However, there is limited knowledge on whole-brain structural alterations present in preterm infants at term-equivalent age when compared to full-term born infants. Diffusion-weighted imaging MRI allows in vivo visualisation and quantification of white matter microstructure and study of whole-brain structural connectivity. Using a whole-brain connectome approach, we aimed to study the impact of prematurity on neonatal brain structural network organization at term-equivalent age.

METHODS

13 full-term (FT) and 24 very preterm newborns at term-equivalent age (VPT-TEA) underwent an MRI (3T Siemens Prisma) examination including diffusion tensor imaging (DTI) (TE=84ms, TR=7400ms, voxel size 2x2x2mm3, gradient applied in 30 non-collinear directions with b-value 1000 s/mm^2 and one non-diffusion weighted image) and T2-weighted image (TE=151ms, TR= 4990ms, voxel size 0.8x0.8x1.2mm^3) acquisitions. The T2-weighted brain volumes were bias corrected, skull striped and tissue segmented into white matter (WM), grey matter (GM), deep grey matter (DGM), cerebrospinal fluid (CSF) and cerebellum using a neonatal-specific segmentation algorithm.[19] Parcellation into cortical and subcortical regions was obtained using the advanced normalization tools (ANTs) (http://picsl.upenn.edu/software/ants) to propagate the UNC neonatal brain atlas[20] into each subject's native space, producing a total of 90 regions, which represents the nodes of the structural networks. Diffusion data were preprocessed using FSL v5.0.10 diffusion toolbox[21,22] and distortions caused by motion and eddy currents were corrected using EDDY function adapted for neonatal data.[23,24] Whole-brain tractograms were generated using probabilistic single-shell, single tissue constrained spherical deconvolution (SSST-CSD) tracking, performed using MRtrix3[25] iFOD2, anatomically constrained tractography (ACT) and backtrack re-tracking algorithms, with streamlines seeded dynamically throughout the WM, producing 1000 million streamlines per subject. The reconstructed data was then further processed using spherical-deconvolution informed filtering of tractograms (SIFT1) algorithm, producing for each subject 10 million streamlines. The resulting set of streamlines were combined with the anatomical node parcellation images, in order to construct, per subject, the structural brain network, an 90x90 interregional connectivity matrix, which were evaluated as binary or weighted by the number of streamline counts (SC) and fractional anisotropy (FA). Graph theoretical analysis of weighted connective matrices was performed using Brain Connectivity Toolbox (BCT) for Matlab.[26] Differences between groups were accessed with the non-parametric Mann–Whitney U test using IBM SPSS Statistics. In order to evaluate structural connectivity strength differences between groups, we performed hypothesis tests at the connection level with false discovery rate (FDR) control with 100.000 random permutations.[27,28] Additionally, we identified the hubs for each group using the group binary representative matrix, where hubs were defined as the nodes with degree superior to the average nodal degree plus 1 standard deviation.

RESULTS AND DISCUSSION

Regarding graph analysis, both VPT-TEA and FT infants' networks (FA and SC-weighted) had a small-world organization. However, in comparison to FT newborns, VPT-TEA infants' structural networks had a statistically significant higher clustering coefficient in SC-weighted networks (p=0.045), but lower characteristic path length (p=0.018) and global efficiency (p=0.006) in FA-weighted networks (Fig.1). In addition, modularity analysis of the SC-weighted networks showed no significant difference regarding the number of modules between groups, but a significantly higher modularity index (p=0.037) in VPT-TEA infants, when compared to FT infants, supporting a larger number of intra-connections, but lower number of inter-connections between modules in VPT-TEA infants. These results reveal that preterm birth is associated with a higher segregation but lower integration of brain structural networks at term-equivalent age. Furthermore, we found that VPT-TEA infants presented 10 nodes with lower nodal strength in the SC-weighted networks. These nodes comprise 6 frontal regions (mainly located in orbito-frontal cortex), as well as right posterior cingulum, right caudate and the thalamus bilaterally (Fig.2). Both FT and VPT-TEA connectomes revealed a right-tailed nodal degree distribution, supporting the presence of hubs, but FT infants' networks evidenced 9 hubs with an averaged nodal degree of 55.11, whereas VPT-TEA infants' networks had 14 hubs with a diminished averaged number of connections, 48. Therefore, VPT-TEA infants evidenced an increased number of hubs, with diminished averaged number of links, compared to FT infants. The hub regions comprised mainly subcortical, limbic and parietal nodes for both groups. Noticeably, VPT-TEA infants had a temporal hub not present in FT, whereas FT had a frontal hub, not present in VPT-TEA infants (Fig.3). Additionally, in comparison to FT, VPT-TEA infants SC-weighted networks presented 66 networks with a statistically significant decreased structural connectivity strength (p<0.05), comprising mostly frontal-cortical/subcortical connections as well as limbic and para-limbic-cortical/subcortical connections (Fig.4).

CONCLUSION

Overall, we reveal that hallmark organization of the adult human brain connectome is present in both FT and VPT-TEA infants. However, VPT-TEA infants' structural networks present a different topological organization, with an increased segregation and decreased capacity to integrate information across brain regions. In particular, VPT-TEA infants evidenced a diminished number of structural connections in subnetworks localized mainly in frontal and also limbic and para-limbic regions.

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Figures

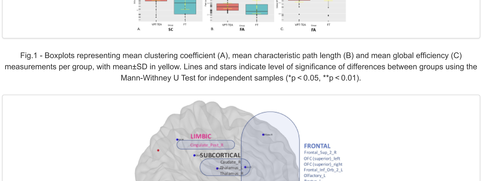

Fig.1 - Boxplots representing mean clustering coefficient (A), mean characteristic path length (B) and mean global efficiency (C) measurements per group, with mean±SD in yellow. Lines and stars indicate level of significance of differences between groups using the Mann-Whitney U Test for independent samples (*p < 0.05, **p < 0.01).

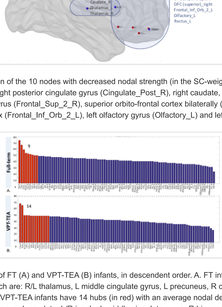

Fig.2 - Brain sagittal representation of the 10 nodes with decreased nodal strength (in the SC-weighted networks) in VPT-TEA vs FT infants. These nodes comprise the right posterior cingulate gyrus (Cingulate_Post_R), right caudate, the thalamus bilaterally and 6 frontal regions: dorsal superior frontal gyrus (Frontal_Sup_2_R), superior orbito-frontal cortex bilaterally (OFC(superior)_left and right), left inferior orbito-frontal cortex (Frontal_Inf_Orb_2_L), left olfactory gyrus (Olfactory_L) and left rectus gyrus (Rectus_L).

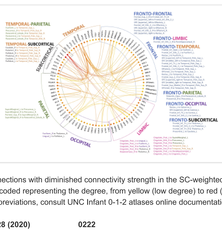

Fig.3 - Nodal degree distribution of FT (A) and VPT-TEA (B) infants, in descendent order. A. FT infants have 9 hubs (in red) with an average nodal degree of 55.11, which are: R/L thalamus, L middle cingulate gyrus, L precuneus, R caudate, R middle cingulate gyrus, L olfactory, R insula and L caudate. B. VPT-TEA infants have 14 hubs (in red) with an average nodal degree of 48, which are: R/L thalamus, R middle cingulate gyrus, L hippocampus, L caudate, L/R insula, L middle cingulate gyrus, R hippocampus, L precuneus, R caudate, L/R putamen and L superior temporal gyrus. L-left, R-right.

Fig.4 - Representation of the 66 connections with diminished connectivity strength in the SC-weighted network, in VPT-TEA in comparison to FT infants. Nodes are color-coded representing the degree, from yellow (low degree) to red (high degree) colour range. For abbreviations, consult UNC Infant 0-1-2 atlases online documentation.