Preterm adolescents have altered hub regions

Introduction:
Extremely preterm birth (<27 weeks of gestation) has been linked to white matter abnormalities in infants [1] but the functional implications of these abnormalities are poorly understood. Thus, the long-term effect of these alterations on adolescents needs further investigation. Brain white matter wiring can be represented by a network of all possible pairwise connections between regions of the brain. Such representation provides valuable insights about the structure of the brain-network. Specifically, in this work, we analyse the hub structure of extremely preterm (EP) born subjects compared to their full term (FT) born social-economically matched peers. Because of their role as focal points for the information transfer in the network, any dysfunction of hub regions may have disproportional effect on the integrity of the remaining network. In the present analysis, we aim to investigate if the EP birth leads to altered hub brain structure.

Methods:
Diffusion-weighted MRI volumes were corrected for thermal noise, Gibbs-ringing artefact and eddy current-induced distortion as well as subject movements artefacts. T1-weighted images were bias corrected using N4ITK algorithm. Tissue parcellations of the corrected T1-weighted volumes were obtained using Geodesic Information Flow (GIF) [2]. We applied Constrained Spherical Deconvolution (CSD) [3] algorithm to estimate the Fiber Orientation Distribution (FOD) in each voxel and performed Anatomically Constrained Tractography (ACT) [4]. From GIF template, we consider 121 unique brain regions as nodes V of network G(V, E). The connection E between each node region V is quantified after applying Spherical-Deconvolution Informed Filtering of Tracks (SIFT2) [5]. Weighted structural networks were computed for 81 EP born adolescents (51 females, 30 males) along with 50 FT born adolescents (30 females, 20 males) as in [6].

Different brain regions are identified as hubs depending on the specific centrality measure applied. To devise a more robust identification of these regions we propose a consensus-based approach by combining rankings across centrality measures as in [7]. We perform a consensus classification for each average network of EP and FT born subjects. Hubs display a high level of connectivity strength $S(j)$ and high betweenness centrality $B(j)$ as well as high nodal efficiency $E_{nodal}(j)$. Each node is assigned a score of one each time 1) the node is in the top 25% of nodes with stronger $S(j)$, or 2) it is placed in the top 25% of nodes with highest $B(j)$, or 3) highest $E_{nodal}(j)$. With a maximum of 3 scores, nodes
that scored 2 or higher are classified as hubs. Figure 1 shows the main steps of identification of the hubs. Statistical analysis is performed to detect group differences regarding $S(j)$, $B(j)$ and $E_{nodal}(j)$ values in the identified hubs. The statistical analysis is performed using student t-test. In addition, group and gender membership as well as brain volume may be confounding variables in the analysis. There is difference in brain volume between females and males as well as between EP and FT born subjects as shown in figure 2. To account to this, we devise 4 nested GLM models, where we compare the full model (the model containing all regressors) to a set of restricted models. Specifically:

1. $Y = \beta_0 X_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \epsilon$
2. $Y = \beta_0 X_0 + \beta_1 X_1 + \beta_2 X_2 + \epsilon$
3. $Y = \beta_0 X_0 + \beta_1 X_1 + \beta_3 X_3 + \epsilon$
4. $Y = \beta_0 X_0 + \beta_1 X_1 + \epsilon$

where $X_1$, $X_2$ and $X_3$ are the regressors for the brain volume, the group membership and gender membership respectively, $Y$ is the mean value of the graph metric under analysis. We compare the nested model fit to the graph metrics that showed a statistically significant difference between the two groups and investigate whether the effect on the graph metric is induced by volume difference, group or gender membership.

**Results:**

The putative hub regions identified for EP and FT born groups are shown in figure 3. There is an overall agreement between the two groups. The statistical analyses indicated that there is a significant decrease ($p=2.6e^{-8}$) in hubs nodal strength $S(j)$ in EP ($\mu =8.9 \pm 1.1$) with respect to FT ($\mu =10.3 \pm 1.3$) born subjects. To a lesser extent, the nodal efficiency $E_{nodal}(j)$ is reduced ($p=1.7e^{-4}$) in EP ($\mu =0.23 \pm 0.03$) with respect to FT ($\mu =0.21 \pm 0.03$). The betweenness centrality $B(j)$ is comparable ($p=0.3$) between EP ($\mu =0.105 \pm 0.010$) and FT ($\mu =0.104 \pm 0.009$). The F test analysis on nested GLM models revealed that brain volume and group membership (model 3) are the most accurate to describe the variance in $S(j)$ and $E_{nodal}(j)$ (top figure 4). The brain volumes describe 37% and 29.5% of the variance in $S(j)$ and $E_{nodal}(j)$ respectively. The group membership accounts for 12% of the variance in $S(j)$ and 4.4% of the variance in $E_{nodal}(j)$ (bottom figure4).
Figures:

Figure 1 Outline of the main steps to perform consensus hub identification.

Figure 2 The distribution of the brain volume for FT born females and males as well as for EP born females and males.
**Discussion**

Different brain regions are identified as hubs depending on the graph metric used; we proposed a consensus method based on $S(j)$, $E(j)$ and $B(j)$. The method revealed overall agreement between the control group and the EP born subjects. In addition, the identified putative regions are consistent with previous studies [7] on healthy subjects by identifying bilateral caudate, thalamus, putamen, precuneus, superior frontal gyrus and precuneus. In addition, the statistical analysis revealed that, although the EP and FT born subject have comparable hubs regions, the hubs in the EP group have a statistically significant reduced connectivity strength as
well as nodal efficiency, while the betweenness centrality is not altered. The F test on nested GLM models suggests that the observed difference is due to brain volume difference as well as EP birth. The analysis of variance on model 3 suggests that although the brain volume influence is greater, the prematurity is significant to induce lower S(j) and Enodal(j). Overall, the results suggest that while the core structure of the EP born brain is preserved, the connectivity and capacity of information flow is reduced and that is linked to reduced volume as well as EP birth.

References