# Functional connectivity differences in full-term and preterm at term equivalent age newborns.

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**Target Audience :** Neuroscientists, Pediatricians, Neonatologists, Engineers

**Purpose :**
There is a growing interest in the nature of spontaneous brain activity observed during so-called "resting state". Specifically, using resting-state functional magnetic resonance imaging (RS-fMRI) it is possible to establish resting-state networks (RSNs) that show temporally coherent (typically low-frequency) BOLD signal fluctuations. There is a growing evidence corroborating the hypothesis that RS functional connectivity is related to both underlying structural connectivity and modulated by the development of white matter pathways occurring early in brain development that are maturing throughout childhood[1]. Nevertheless, only few studies have investigated resting-state connectivity and its development in infants, and much less have compared RSNs in full term and premature newborns at term equivalent age (TEA). In their study, Smyser and collaborators[2] used seed component analysis based on predefined regions of interest to show weaker network connectivity in preterm babies at TEA. However, more studies without seed selection are needed to answer the question to which extent premature exposure to extra-uterine environment impacts on functional connectivity during resting state of the human brain.

**Methods :**
Population: Nineteen healthy term newborns (mean gestational age: 39.75 weeks ±0.99) at 3-4 days of life and thirteen premature babies (mean gestational age at birth: 28.90 weeks ±1.95) at TEA (mean gestational age during MRI: 40.39 weeks ±0.71).

Acquisition: We acquired 8 minutes of RS-fMRI (EPI sequences on a Siemens 3T scanner: TR=1600ms, TE=30ms, 30slices, voxel size=2.5x2.5x3.0mm$^3$) during natural sleep or while resting quietly in the scanner without any sedation. 300 volumes have been obtained using neohead coil (12 term and 2 preterm infants) or 32 channels head coil (7 term and 11 preterm newborns). No difference was found between the two types of coils.

Preprocessing: RS-fMRI data were realigned; coregistered with the T2 structural image; normalized to a T2 template made with 20 term and preterm at TEA infants; and smoothed using an isotropic Gaussian kernel (6 mm full width at half maximum). All volumes with an absolute displacement from frame-to-frame higher than 0.5mm were removed and remaining images have been concatenated. If more than 25% of the volumes were contaminated by motion, children's data were not included in the analyses.

Analysis: Data from both groups have been decomposed into fifteen relevant components (number of components estimated using MDL algorithm) in a single group-level independent component analysis (ICA) using GIFT package. A mask, based on newborns template segmentation, has been used to remove cerebrospinal fluid, ventricles, eyes and extra-cerebral areas. ICA was repeated 20 times using ICASSO to ensure stability of the decomposition.

Resting-state network connectivity matrices were built by calculating Pearson correlation between the timecourses for the 105 pairs of components. A two sample t-test was performed for each pair to assess difference between the two groups (p<0.01 corrected for multiple comparison using Bonferroni correction). The same test was also performed between newborns recorded with both coils.

Pearson correlation analysis between the functional network connectivity and gestational age (across groups) has been done to test influence of gestational age (p<0.01, FDR-corrected).

**Results:**
The overall group-level analysis revealed functional networks located in cerebellum (1), occipital (visual) (2), prefrontal (3), anterior cingulate cortex (ACC) and insula (4), temporal (auditory) (5), sensorimotor cortex (6), Cuneus (7), precuneus (8), brain stem (9) and superior frontal and dorsal ACC (10) (Fig1). Functional connectivity between the auditory component (5) and ACC-insula component(4) was significantly different between term and preterm infants. In preterm babies, the timecourses of BOLD oscillations within these two components were anti-correlated whereas in term infants, they were positively correlated. Furthermore, the correlation coefficient between these two components measured at term also indicates correlation with gestational age at birth (Fig 2).
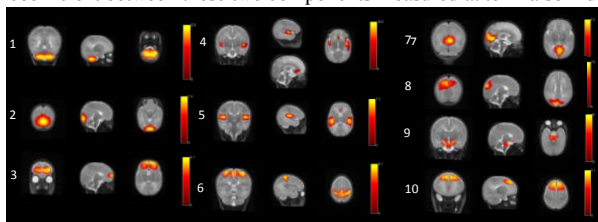


**Fig 1.** Each row shows in a coronal, sagittal and axial view resting-state networks. They are thresholded at Zscore > 3 superimposed on a T2-weighted MR infant brain template. The color-bars show the corresponding Zscore.
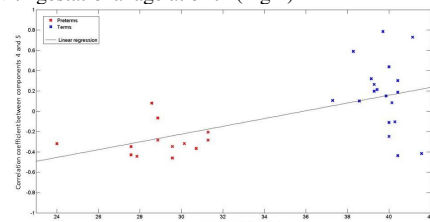


**Fig2.** Scatter plot of gestational age versus functional network connectivity between auditory (5) and ACC-insula (4).

**Discussion and conclusions:**
Networks found are consistent with those previously described in infants[3] and most of them have been found in adults.

In contrast to earlier studies this study uses seed independent groups level ICA to compare functional connectivity between full term infants at 3-4 days of life and premature infants at TEA. Network correlations are important measures of brain processing and evolve with brain development from childhood to adulthood. As an example, anti-correlation between default mode network and dorsal attention does not exist at birth but can be seen at 1 year of age[4] and correlation between medial and dorsal prefrontal cortex turns from being positive in children to negative in adults[5]. Furthermore, posterior insula is known to be connected to sensory areas, allowing integration of sensory information whereas anterior insula is linked to ACC and limbic structures, thus bringing salience detection. This second network is usually called "salience network" in resting state fMRI. In adults these two networks seem to be anti-correlated[6]. We observed different correlations in premature and full term babies between a sensory area (Auditory network) and the salience networks. Actually, preemies show an anti-correlation between these networks whereas in term infants they are positively correlated. However a larger cohort is needed to assess to what extent neonatal experience influence on functional connectivity between Auditory and Salience network.

**References:**
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