The Funcitonal-structural Interplay during First Two Years' Brain Development

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Introduction

While several studies have demonstrated the potential links between brain structural (DTI) and functional (resting BOLD) connectivity, all of the studies thus far have focused on adults, making it difficult to determine whether or not this link truly reflects the relation between functional and structural connectivity[1, 2]. To better delineate the interplay between functional and structural connectivity, the presence of temporal alterations of both functional and structural connectivity during the first years of life may offer an excellent experimental model to rigorously determine the relation between functional and structural connectivity. In this study, normal and healthy pediatric subjects aged between 2wk to 2 yrs were studied so as to directly compare the temporal evolution of brain functional and structural connectivity. In so doing, we aim to determine the temporal correlation between functional and structural connectivity during the first two years of life and to reveal whether or not maturation of structural connectivity is needed for functional connectivity.

Methods

A total of 123 normal subjects, including 42 neonates (20M, 21 $\pm$ 11 days (SD)), 40 1yr olds (21M, 13 $\pm$ 1 mon), and 41 2yr olds (24M, 24 $\pm$ 1 mon) were included in this study. In addition, 16 normal adult subjects (11M, 25~35yrs) were also recruited for comparisons. All pediatric subjects were at sleep without sedation during the imaging session. Informed consent was obtained from the parents and the experimental protocols were approved by the institutional review board.

All subjects completed the rfcMRI studies using a T2*-weighted EPI sequence with TR = 2sec, TE = 32 ms; 33 slices; and voxel size = 4x4x4 mm^3. 150 volume data were acquired to provide time series images. A subset of subjects (14 neonates, 18 1yr olds, 27 2yr olds and 15 adults) also completed 6-direction DWI scan with b-value 1000 mm^2/s, TR/TE=7500/73 ms; slice thickness=2 mm and an in-plane resolution=2*2 mm^2. Anatomical images using a 3D MP-RAGE sequence were also acquired for all subjects with TR = 1820ms; TE = 4.38 ms; inversion time = 1100ms; 144 slices; and voxel size = 1x1x1mm3.

Preprocessing of rfcMRI data included time shifts, rigid body correction for head movement, spatial smoothing (6-mm FWHM Gaussian kernel) and low pass filtering (<0.08Hz). Data in each age group was subsequently normalized to a longitudinal data set at the corresponding time point (2wk, 1yr- and 2yr-old) using the transformation field acquired from T1 nonlinear registration. After calculating the tensor, the DTI images were also warped to the same space. Subsequently, group independent component analysis (ICA) [3] was performed on 2yr olds' data yielding a set of components, reflecting brain functional connectivity. Spatially unconnected regions of the identified independent components were extracted as individual ROIs. This set of ROIs was used as template and warped to neonates', 1yr olds' and adults' space, respectively, to facilitate group comparison.

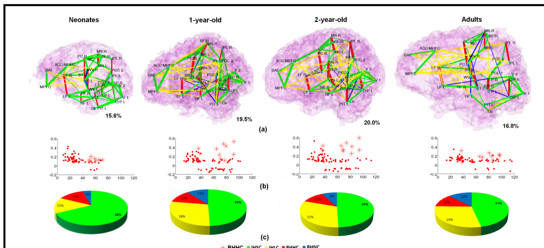

Fig.1 Whole brain functional connectivity pattern at all 4 age groups.

The mean time series from each of the 30 defined ROIs was extracted from individual subject within each age group to construct a 30*30 partial correlation matrix describing the whole brain connectivity pattern. Partial correlation was applied here to detect more direct interactions. Subsequently, the individual matrix was Fisher-Z transformed and averaged to obtain a group-mean functional connection (FC) matrix for each age group and student-t test was performed to detect connections that were significantly different from zero after correcting for multiple correction (FDR, $p<0.05$). To explore possible structural correlates with the functional connectivity, all connections were divided into four subcategories according to their spatial characteristic as intra-hemisphere short-distance connections (IHSC, green), intra-hemisphere long-distance connections (IHLC, yellow), between-hemisphere homologous connections (BHHC, red) and between-hemisphere non-homologous connections (BHNC, blue). For structural connectivity assessment, whole brain fiber tracking was performed on the mean DTI image from each age group and the mean FA values along the fibers that pass through a pair of ROIs were calculated from each individual subject to represent the structural connection (SC) strength between them, which was then similarly averaged as that for FC to obtain a mean SC matrix for each age group.

Results

The whole brain functional connectivity is presented in Fig. 1, including the anatomical location and functional connectivity patterns along with the connection density (lower right of each brain) for all age groups in Fig. 1a, the relation between the connection strengths and the corresponding anatomical distances (Euclidean distance between the centers of the pair of regions) in Fig. 1b, and the distribution of all FCs in relation to the 4 categories: IHSCs, IHLCs, BHHCs, and BHNCs in Fig. 1c, respectively. Together, these results offer three major findings. First, the whole brain is already functionally synchronized in neonates as a "connected" network with no "isolated" regions although their connection density (15.6%) is the lowest. Second, the relation between the strengths of FCs and anatomical distance roughly follows an inverse distance square law with the exception of the BHHC connections (red asterisks, Fig.1 b) where the connection strengths are elevated starting from neonates. Finally, the percent of IHSC is dramatic decreased with a concurrent increase in IHLC and BHNC from neonates to 1yr olds. The IHSCs dominate at neonates (68%) but decrease dramatically to less than 50% thereafter. In contrast, long-distance (IHLC) and non-homologous connection (BHNC) percentages start low in neonates (15%+4%= 19%) but are more than doubled to 39% (28%+11%) in 1yr olds and remain similar thereafter.

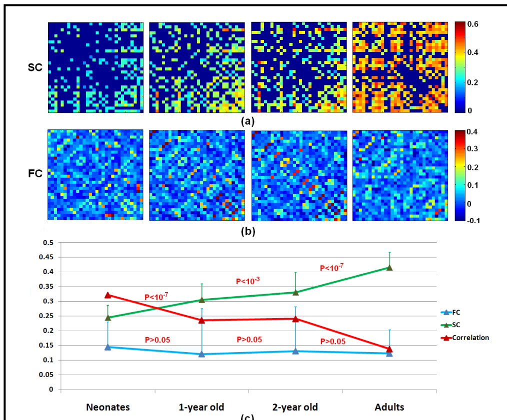

Fig.2 Structural correlates of functional development

The mean SC/FC matrices are shown in Fig. 2 (a, b). Generally, SC values increase with age but the FC values do not exhibit a clear increasing pattern with age (Fig. 2c). As a result, it is not surprising that the correlation between FC and SC decreases with age (Fig. 2c, red curve); it starts fairly high at around 0.33 in neonates, noticeably decreases to around 0.24 in 1yr olds, remains similar in 2yr olds, but decreases dramatically to around 0.14 in adults.

Discussion

Interesting patterns of the interplay of functional/structural connectivity during early brain development are observed. As shown in Fig 1c, the majority of FCs in neonates are IHSCs. However, the percent of IHSCs is substantially reduced with a concurrent increase of IHLCs in 1yr olds. This change of percents in IHSC and IHLC coupling with the increased SC values from neonates to 1yr olds suggest that the maturation of the major white matter may play a critical role in establishing long distance functional connectivity. Interestingly, however, the SC values continue to elevate after 1 yr of age (Fig. 2c), yet the distribution of different categories of functional connectivity (Fig. 1c) and the strengths of FCs (Fig. 2c) remain rather stable through the adulthood. In fact, the correlation between SC and FC continuously decreases with age. These findings are somewhat surprising since one would expect that the continuing maturation of white matter (SC) should further facilitate functional connectivity. Closely examining our results in Fig. 2a and 2b, it appears that the elevation of SCs is more uniform throughout the entire brain while the changes of FCs appear to be more regional, leading to a reduction in correlation. That is, after the 1yr of age, regionally selective maturations of FCs, which may reflect functional specializations, are the main processes for FC while the maturation of SC is more homogeneous throughout the entire brain. Future studies focusing on specific functional connections will need to be conducted to further elucidate the relation between FC and SC in the individual brain regions.

References

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