Multi-layer Large-Scale Functional Connectome Reveals Infant Brain Developmental Patterns

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Abstract. Understanding human brain functional development in the very early ages is of great importance for charting normative development and detecting early neurodevelopmental disorders, but it is very challenging. We propose a ***group-constrained***, ***robust*** community detection method for better understanding of developing brain functional connectome from neonate to two-year-old. For such a multi-subject, multi-age-group network topology study, we build a ***multi-layer*** functional network by adding inter-subject edges, and detect modular structure (communities) to explore topological changes of multiple functional systems at different ages and across subjects. This "Multi-Layer Inter-Subject-Constrained Modularity Analysis (MLISMA)" can detect group consistent modules without losing individual information, thus allowing assessment of individual variability in the brain modular topology, a key metric for developmental individualized fingerprinting. We propose a heuristic parameter optimization strategy to wisely determine the necessary parameters that define the modular configuration. Our method is validated to be feasible using longitudinal 0–1–2 year's old infant brain functional MRI data, and reveals novel developmental trajectories of brain functional connectome. This work wassupported by the NIH grants, EB022880, 1U01MH110274, and MH100217.

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1 Introduction

Human infant brain is a rapidly developing complexity both structurally and functionally. While anatomical changes during the first two years of life have been extensively studied [1], the functional developmental changes in this pivotal stage are

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still elusive. Understanding how the brain is functionally organized as a large-scale "functional connectome" and its evolution in the very early ages will shed light on the behavioral, cognitive, neurophysiological, neurological, and neuropsychiatric studies in the elder ages and facilitate early detection of developmental disorders [2]. However, the studies on the neonatal and early infancy dynamic maturing processes in the scale of whole-brain networks are still scarce [3–6].

There are three major difficulties. ***(1)*** Neonate/infant functional Magnetic Resonance Imaging (fMRI) is noisier than the adults' fMRI, which poses a great challenge to robustly model network topological properties. ***(2)*** Inter-subject variability information is usually lost in traditional averaging-based group-level network analysis, but it is essential for individualized developmental fingerprinting and charting [7]. ***(3)*** For longitudinal studies of brain development, it is difficult to generate temporally consistent network topological properties using traditional cross-sectional network analysis. In this paper, we propose a new method, namely, Multi-Layer Inter-Subject-Constrained Modularity Analysis (MLISMA), for a ***robust*** network community detection with ***well-preserved*** individual variability dedicated for longitudinal functional connectome development studies. MLISMA probes early brain development along the dimensions of space (brain regions and communities), time (age groups), and subject.

In MLISMA, we build multi-layer networks connecting together the data from all subjects at the same age, instead of the traditional, single-layer group-averaged network. A generalized Louvain (GenLouvain) algorithm [8] is applied to detect community structures or modules. The innovation here is two-fold. First, two key parameters that control inter-subject consistency and modular resolution are ***jointly*** optimized based on multiple empirical metrics, instead of an arbitrary parameter selection. We observed that such a multi-task parameter optimization could eventually lead to temporally consistent parameter settings and brain modularity. Second, we can use MLISMA to ***both*** achieve inter-subject consistency ***and*** probe individual variability that represents the unique brain connectome topology for each subject.

To demonstrate the effectiveness of our method, we applied it to characterize developmental changes in modules (reflecting different brain functional systems) in the neonates' and infants' brains based on a 0–1–2 year's old longitudinal resting-state fMRI (rs-fMRI) dataset. The results suggest a different story that the human brain connectome may develop via conservative rewiring that minimally affects the quantity of the brain functional networks. The individual variability in modular structure may significantly decrease from neonate to 1-year-old and keep stable at 2-year-old. Furthermore, we detect the brain regions with large inter-subject differences in modular participation and their spatiotemporal changes during development. The results provide potential targets for neurodevelopmental monitoring for early abnormality detection.

2 Materials and Methods

2.1 Multi-layer Network

Each subject's brain functional network can be represented by a functional connectivity (FC) matrix or adjacency matrix with each element representing temporal synchronization

of rs-fMRI blood-oxygenation-level-dependent (BOLD) signals from a pair of spatially distant brain regions. Traditional network neuroscience analyses predominantly focus on either each subject's FC matrix or a group-mean FC matrix averaging across all subjects [9], each of which essentially transforms the data into a ***single-layer*** network analysis that might blur the network topology, be sensitive to individual noise, and can neither detect nor account for individual variability.

By adding edges linking corresponding nodes of different single-layer networks, a multi-layer network can be constructed [10]. Figure 1 shows a schematic illustration of the modularity analysis based on a multi-layer network constituted by 3 subjects, each having a 7-node 2-module FC network. By adding inter-layer edges between each subject pair, we create a multi-layer network that corresponds to a bigger "supra-adjacency matrix". Compared to the single-layer network, a multi-layer representation has many good properties. ***(1)*** It allows a group-level network analysis while considering every single network's contribution. ***(2)*** It makes use of inter-subject constraints

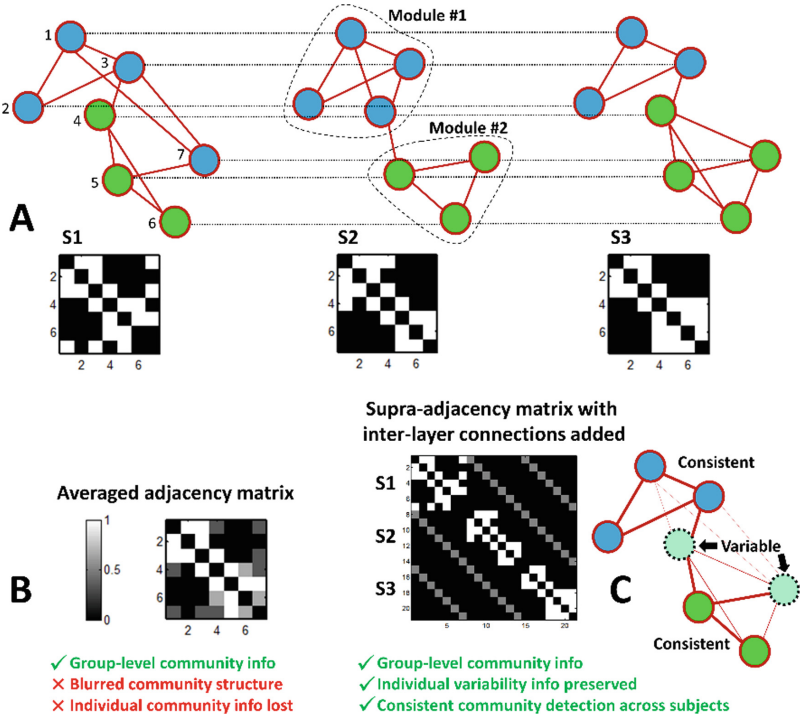

Fig. 1. Illustration of the module detection from a supra-adjacency matrix with each subject's adjacency matrix in the diagonal blocks and inter-layer (inter-subject) connections added. **(A)** A simple illustration of 3 subjects' FC networks and their corresponding adjacency matrices with different modular configurations. **(B)** A group averaged adjacency matrix with blurred community structure. **(C)** A multi-layer network (the connectivity strength across different subjects is set to 0.5 in this example), based on which group-consistent modules are detected and the nodes with consistent and variable modular assignment across subjects can be determined.

to achieve robust and consistent modular detection. ***(3)*** Under the premise of group consistency, each subject's network properties (e.g., modularity) can be individually evaluated while simultaneously contributing to the global population-level analysis, allowing individual variability analysis.

2.2 Multi-layer Network-Based Modularity Analysis

Various network metrics can be calculated to describe multi-layer network properties [10]. For brain functional connectome study, one of the most important metrics is network communities, or modules [11]. The brain network modular organization can be derived from a graph partition based on network topology by maximizing the modularity quality function (Q) as has been typically used to optimize the concentration of the FC edges within the modules [12]. The modules naturally represent various functional systems, each of which has independent function. For development studies, understanding how modules change spatiotemporally is a key for understanding how different functional systems develop and how functional segregation/integration evolve [13].

This is the first study using multi-layer network-based modularity analysis to reveal brain functional development in the early life (from neonate to 2-year-old). One of the most important questions in developmental neuroscience is how different neonates have different brain network structures and their developmental trajectories that make each subject different from others. Therefore, assessment of the individual variability in the network topology in such a pivotal period of life is essential for both normative charting and early abnormality detection. In this paper, we proposed ***MLISMA*** (Multi-Layer Inter-Subject-Constrained Modularity Analysis) for this purpose. The flowchart is depicted in Fig. 2, which consists of 4 steps:

Step-1 (Multi-layer Network Construction): We construct each subject's FC network based on pair-wise correlation of regional rs-fMRI time series. We then build a multi-layer network for each age group by adding cross-layer edges connecting corresponding brain regions between any pair of subjects of the same age. This exerts an inter-subject consistency constraint to the subsequent module detection.

Step-2 (MLISMA Module Detection): GenLouvain [8, 14] was used to group brain regions across all subjects in each age group into group-level modules. Two important parameters that exert a significant effect on the detected modules are the resolution or scaling parameter (γ) and inter-subject coupling parameter (ω). Previous adult brain connectome studies often used selected, fixed values of γ and/or ω [15], the selections of which risk accidentally ignoring the fundamental, underlying network topology patterns. One recently developed strategy for selecting the parameters was presented in [16]; however, in this work, we sought to more directly select the parameters according to multiple modularity metrics for our data. To this end, we devise ***Heuristic Parameter Optimization***, based on the number of modules (K) and the individual variability in modular structure (inversely proportional to NMI, normalized mutual information of whole-brain modular participation averaged pairwise across all subjects). During this procedure, the stochastic nature of the GenLouvain algorithm was considered. Developmentally-consistent parameters are

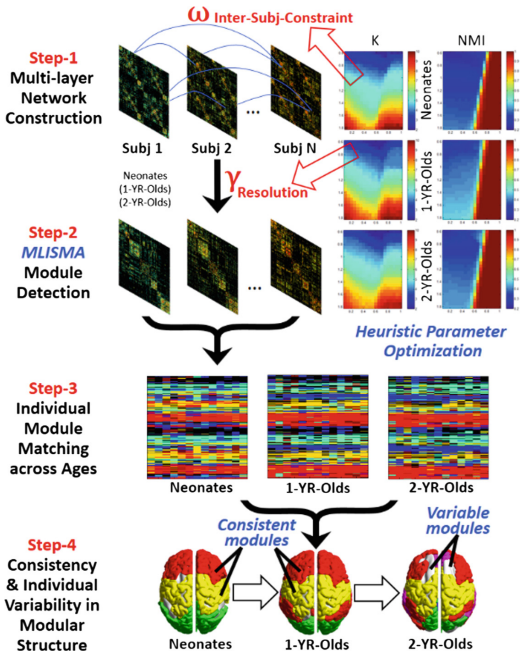

Fig. 2. Flowchart of Multi-Layer Inter-Subject-Constrained Modularity Analysis (MLISMA) and its application to infant's brain functional development study. The entire framework consists of 4 steps from the construction of multi-layer networks to the detection of consistent and variable modular belongingness for each brain region. A "Heuristic Parameter Optimization" strategy (detailed in main text) is proposed to determine the two key parameters in such a multi-subject, multi-age-group modular structure analysis. MLISMA introduces a group constraint to individual-level module detection, allowing robust determination of the individual-level modules with group correspondence and consistency toward individual variability analysis.

determined according to the heatmaps in the parameter plane. For each age group, all subjects' modules are generated.

Step-3 (Module Matching across Ages): After obtaining the group-constrained individual modules, group-level modular matching is conducted to match corresponding modules across different age groups for the following post-analysis.

Step-4 (Consistency & Individual Variability Analysis): Specific brain regions with variable modular assignment across all subjects of the same age can be detected by focusing on individual modular structures as output from GenLouvain. We detect ***both*** regions with group-consistent modular assignment ***and*** regions with high individual variability in modular assignment (e.g., by calculating whether more than 50% subjects have the same modular attribute on the same brain region).

2.3 Heuristic Parameter Optimization

It is essential to optimize γ and ω ***jointly*** and ***reasonably***. Both parameters will affect each other's optimal setting, thus, they should be estimated jointly. They should lead to

reasonable network modular configurations based on the following criteria. We calculate heatmaps of *K* and *NMI* by varying γ and ω. Since GenLouvain can produce a stochastic result, we repeat the calculation 100 times at each set of parameters to generate averaged heatmaps. The three age groups show astonishingly similar patterns (Fig. 3). We regard extremely small or large modular quantity ($K < 4$ or >10) and extremely little individual difference ($NMI > 0.7$) as unreasonable results based on the widely accepted previous findings [3, 4, 11, 13, 15]. According to the leftover area in the *K* and *NMI* heatmaps, we determine a zone of parameters for which we are confident about the results and select γ and ω as the center. The result of parameter selection is also assessed with *Q* heatmap, showing reasonable and consistent across the age groups.

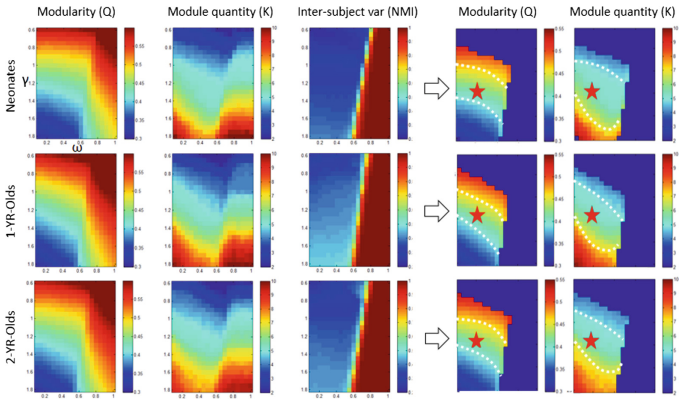

Fig. 3. Heuristic Parameter Optimization. Heatmap-based joint optimization of γ and ω based on module quantity (*K*) and inter-subject similarity (*NMI*). The dark blue areas in the right panel indicate unreasonable parameter combinations. The stars are the optimized values of γ and ω.

2.4 Post-MLISMA Analysis

Different measurements can be employed to qualitatively and quantitatively evaluate developmental brain networks, including ***(1)*** a summary of the MLISMA result with color-coded modular index modulated by grey-scale-coded individual variability, ***(2)*** a spatial evolving pattern for each module, ***(3)*** module size evolution that quantifies how many brain regions are included in different modules at each age, and ***(4)*** individual variability changes along development (Fig. 4).

3 Experiments and Results

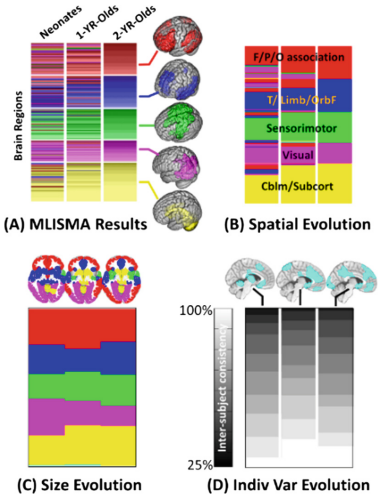

Fig. 4. MLISMA results show different aspects of evolving brain functional networks. Four different following-up analyses are provided for the MLISMA outputs, see details in the main text.

We used natural sleeping rs-fMRI data from "Multi-visit Advanced Pediatric brain imaging study for characterizing structural and functional development (MAP Study)" with repetitive scans on 13 subjects in the ages of 1-week, 12-, and 24-months [17]. Individual FC network was constructed based on a widely used 268-region atlas [18]. The optimized γ and ω were determined as 1.3 and 0.3, respectively. Modularity Q was found to be slightly increased in the first year of life, but modular quantity K was largely stable ($\sim$5). Results indicate relatively stable functional integration/segregation notwithstanding the spatial pattern of modules continuously changes. We found prominently reduced individual variability in the modular structure in the age of one year (Fig. 4D). By visiting each brain region for its modular participation and comparing it among different age groups, we identified three major developmental patterns: ***(1)*** increasing diversity at striatal, frontal, parietal and occipital regions (Fig. 5A), ***(2)*** decreasing diversity at the frontal-temporal-parietal association areas (Fig. 5B, C), and ***(3)*** stable module assignment in the primary visual and motor networks (Fig. 5D). The spatial location of the regions with diverse modular participation across subjects generally move from the medial structures to lateral association areas (especially the default mode network).

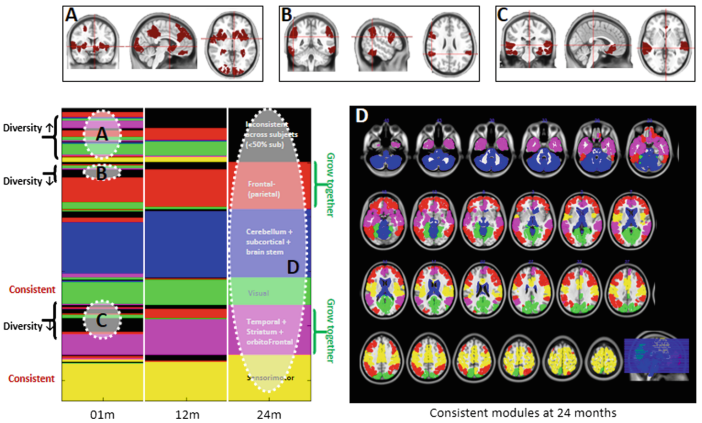

Fig. 5. Regions with increasing and decreasing diversity of modular assignment.

Figure 6 shows quantitative results. ***(1)*** Modular quantity K is stable across different ages. ***(2)*** Modularity Q significantly ($p < 0.05$, corrected) increases from neonate to 1-year-old and keeps stable later. ***(3)*** Individual variability is significantly ($p < 0.05$, corrected) reduced from neonate to 1-year-old and keeps stable thereafter. Interestingly, when assessing the individual variability of modular structure across the brain regions within each lobe rather than the whole brain, we found more developmental details. For example, frontal, temporal and parietal lobes have first increased but then decreased individual similarity, whereas occipital lobe has continuously increased individual similarity in the modular attribute.

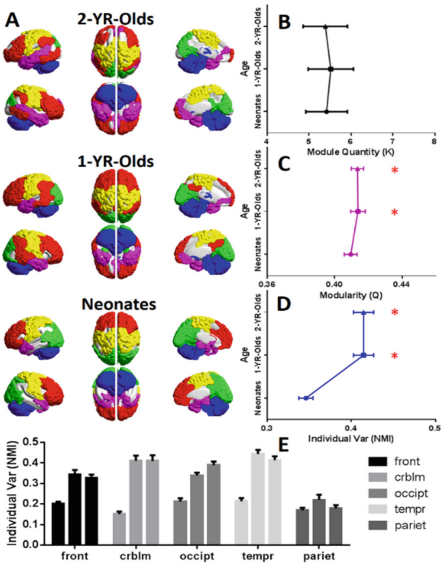

Fig. 6. Modular structure development. Asterisks indicate significant changes.

4 Discussion

MLISMA avoids previous brute-force group averaging-based module detection and achieves subject-consistent module detection result while preserving and respecting individual variability, which is essential for developmental study. We found a stable developmental pattern in terms of modularity, a new finding compared to a previous report with increasing module quantity. We found novel developmental changes in individual variability of modular attributes. Our study indicates that early brain functional development could be rather stable and inherently consistent for maintaining a balance. The individual variability could reflect unique myelination and pruning processes modulated by environmental/genetic factors [4].

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