Developmental Changes in Backbone of Brain Functional Network During the Infancy Period

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ABSTRACT

In a normal development, structure and functions of the infant's brain change efficiently to enable one's communication with the external world. However, it is still a mystery that how dominant connections of the brain network called "backbone" change in the infancy period. In this study developmental changes in the backbone of functional brain network are investigated. Therefore, resting state EEG of 15 infants (7 girls, full-term) with no family health problem were recorded at the ages of 6 and 18 months. Subsequently, the brain functional network was estimated from the cleaned EEG using Weighted Phase Lag Index (WPLI) algorithm. The WPLI network was then explored using the graph theory by Minimum Spanning Tree. Parameters of the MST including diameter, betweenness, leaf number, eccentricity, and hierarchy were calculated. Subsequently, a pairwise t-test was performed based on the MST parameters to compare backbone of the brain network between both age groups. Based on the Power Spectral Analysis, four frequency bands including delta, lower alpha, lower beta, and gamma bands were selected, each of them investigated separately. The results showed an increase of eccentricity and diameter, and a reduction in leaf numbers, betweenness and hierarchy (lower complexity) in the functional networks of the frequencies with enhanced power (eg. gamma). In addition, opposite results were observed in the networks related to the frequencies with declined power (eg. delta). Our findings indicate that backbone of the brain functional network changes in a frequency specific manner, and a reverse order follows the changes in oscillatory pattern.

Key Words: Glioma, pathogenic, biomarker, therapeutic, prognosis, diagnosis

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Introduction

Human's brain is comprised of many nerve cells and the connections between them. The changes and the growth of neuron connections are called "brain development." Brain development is depended on many factors and processes. Scientists are increasingly interested in understanding the steps and factors that build a healthy brain to recognize the disorders of brain development, and the clues about how to repair the brain following an injury (Marsh *et al*., 2008; Wu and Sun, 2015). However, development of central nervous system in infancy period still needs to be better understood. In this context, utilizing advanced technologies can help us to measure changes of brain's network topography in the course of its developmental stages. Various types of neuroimaging or electrophysiological recording methods such as electroencephalography (EEG) (Schetinin and Jakaite, 2017; Tomalski *et al*., 2013), Functional Magnetic Resonance Imaging (FMRI) (Holland *et al*., 2014; Van Horn and Pelphrey, 2015) and magnetoencephalography (MEG) (Eswaran *et al*.,

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2004) have been applied for this purpose. In addition, a wide range of techniques have been applied for the data analysis. Studies based on functional connectivity have shown that the child's brain first develops local connectivity (Fair *et al.*, 2009; Lebel *et al.*, 2008) and then gradually shifts forward in the direction of long distance connectivity. From another perspective, the child's brain network acts like a graph. Graph theory analysis has played a crucial role in the previous neurodevelopmental studies (Bassett and Bullmore, 2006; Batalle *et al.*, 2012; Boersma *et al.*, 2013; Rapoport *et al.*, 2012). Graphs can be drawn by using various approaches (Sporns, 2003). However, to solve the problem of network comparison, the graph needs to be normalized either by setting a fixed threshold for the edges, or a fixed average degree to obtain a similar level of sparsity in different conditions (Van Wijk *et al.*, 2010). One promising solution to circumvent this problem is the Minimum-weight Spanning Tree (MST) which does not need to fix the number of edges and nodes or a threshold. MST is a unique acyclic sub-graph that connects all nodes, and maximizes properties of interest such as synchronization between various brain areas (Stam CJ *et al.*, 2014). There is a wide range of applications for MST method (Alexander-Bloch *et al.*, 2010; Lee *et al.*, 2006; Lee *et al.*, 2010; Ortega *et al.*, 2008; Schoen *et al.*, 2011), but only limited studies have applied this method to the investigation of brain development. In this study, resting-state EEG was recorded from 15 infants (7 girls, full-term – 37 to 40 weeks from gestation) at 6 months and 18 months after the birth. Then, functional connectivity networks were extrapolated from 32-channel EEG using Weighted Phase Lag Index (WPLI) approach by considering its high level of repeatability (Khadem and Hossein-Zadeh, 2014). Subsequently, the MST analysis was performed on WPLI Martix to determine network parameters including eccentricity, diameter, leaf number, betweenness, and hierarchy. These parameters were used to expand our knowledge of developmental changes in functional brain networks. We hypothesized that the brain network topology has an age specific pattern during the infancy period. Therefore, the aim of this study is to calculate the aforementioned pattern within a band-specific Framework.

This article is organized as follows. First, the material and applied methods are explained. Then, the acquired results based on spectral and functional analyses are presented. Subsequently, a discussion of the statistically significant findings is provided. Finally, a conclusion on the results and some suggestions for future works will be made.

Experimental Section

Subjects

In this study, 15 healthy infants, 37 to 40 weeks from gestation (seven females and eight male infants) with no family history of a neurodevelopmental disorders or maternal depression were recruited. Table 1 presents the demographics of the subjects on the day of birth. The study protocol was approved by the Institute for Cognitive and Brain Sciences, Shahid Beheshti University Review Board. Parents were fully informed and signed the consent form. Samples were taken by trained personnel. Subjects whose mothers were on chemotherapy, psychotropic drugs, including antidepressant or anxiolytic medications, or with type I diabetes mellitus were excluded. The EEG data of all infants were collected twice, first at the age of 6 months and second time at the age of 18 months (within 2 weeks to date.)

Neurophysiological data: EEG recording

EEG data were collected from infants at the ages of 6 months old and 18 months old. The EEG data of eyes open resting-state were recorded by 32 channel eego™mylab (ANT Neuro, Netherlands) with a cap size of N4-04, placed on the surface of the scalp at the 10-20 International System coordinates. All electrodes impedance was checked on-line, and EEG data were recorded with sampling frequency of 1000 HZ. After recording all EEG data, signals were converted to Matlab format to do standard preprocessing pipeline by EEGLAB toolbox (Delorme and Makeig, 2004) and some self-adapted Matlab functions. Preprocessing steps of data included noise reduction of raw signals

Table 1. The demographics of the subjects at the day of birth.

Gender	Girls	Boys	T-value	P-value
Number	7	8	---	---
Gestation Weeks	38±1.15	38.88±0.99	-1.58	0.14
Birth Weight	3127.57±344.08	2971.5±351.85	0.87	0.40
Birth Length	48.96±1.44	48.79±1.41	0.27	0.79
Head Circumference	34.29±1.11	33.19±1.22	1.81	0.09

by a band-pass filter (1-40 Hz); segmenting data to 240 trials of 1 second; artifact removal (Mognon *et al.*, 2011); rejecting bad epochs to improve data quality; interpolating bad channels, and re-referencing to average channels. After preprocessing, the cleaned EEG data was analyzed using the following methods.

Power Spectrum Analysis

Investigation of separate frequency bands plays a crucial role in obtaining high quality results. The selection of these frequency bands was based on the results of power spectral analysis. Power spectrum of the EEG signal was calculated using Fast Fourier Transform (FFT) on each trial to convert time domain to frequency domain in the range of 1 to 40 Hz with a frequency resolution of 0.001 Hz. The relative power spectrum of all 32 channels were obtained by calculating the ratio between power spectrum of each frequency band and the total power of 1-40 Hz. The paradigm of power spectrum analysis is presented in Fig. 1. Based on the significantly changed frequencies, four bands including [1-4], [7-10], [13-23], [30-40] Hz were selected for the functional connectivity analysis.

Functional connectivity

Functional connectivity is simultaneous activities of pairs of electrodes. This measure illustrates functional relationship between different areas of the brain. There are many different linear and nonlinear methods to calculate functional connectivity such as partial correlation(Hlinka, Alexakis, Diukova, Liddle, & Auer, 2010), Phase Locking Value (PLV) (Martini *et al.*, 2012), correlation and pair-wise phase consistency (PPC) (Bastos and Schoffelen, 2016), Weighted Phase Lag Index (WPLI) (Hardmeier *et al.*, 2014; Stam CJ *et al.*, 2007). Among these methods, the WPLI is not influenced by the effects of volume conduction as much as other methods. Therefore, it could represent the brain interactions in a more reliable way. In this study, functional connectivity between different brain regions was estimated by Weighted Phase Lag Index (WPLI) (Khadem and Hossein-Zadeh, 2014).

Weighted Phase Lag Index

The WPLI is derived from Phase Lag Index (PLI) which has been defined as an asymmetric distribution of phase differences between two signals (Ortiz *et al.*, 2012). The PLI range is between 0 and 1 and this phase synchronization measure is minimally affected by volume conduction (Ortiz *et al.*, 2012). The phase consistency can be better measured by WPLI which is less sensitive to noise and has a better signal to noise ratio as compared to PLI (Vinck *et al.*, 2011). The WPLI is calculated in the following steps. First, Fourier Transform and cross spectrum of two real-value signals will be calculated.

$$C(f)=X(f)Y^*(f) \qquad (1)$$

where C denotes the cross spectrum of X(t), Y(t), and $Y^*(f)$ is the complex conjugate of Y(f). for the purpose of frequency range determination, we can consider the complex non-diagonal part of C as Z. Then, PLI is calculated as the absolute value of the sign of imaginary part of Z entitled as J (Stam CJ *et al.*, 2007):

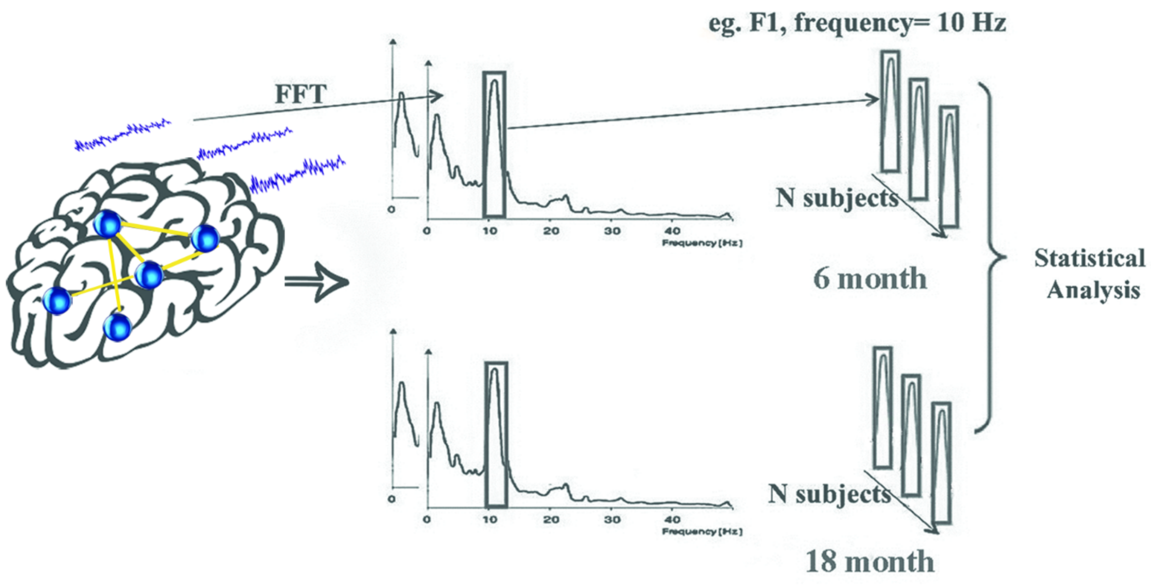

Figure 1. Power spectrum analysis.

$$PLI \equiv |E\{sgn(J(Z))\}| \quad (2)$$

In fact, PLI suffers from discontinuity; therefore, it is difficult to measure changes in phase synchronization using PLI (Ortiz *et al*., 2012). Hence, the WPLI is proposed to overcome this deficiency by placing more weight on the cross spectrum in accordance to the magnitude of imaginary component (Vinck *et al*., 2011).

$$WPLI = \frac{|E\{J(Z)\}|}{E\{J(Z)\}} = \frac{|E\{|J(Z)|sgn(j(Z))\}|}{E\{|J(Z)|\}} \quad (3)$$

It has been shown that neural functional connectivity as well as integrity of the brain network are enhanced while in the process of maturation (Smit *et al*., 2016). Therefore, we decided to apply the extracted WPLI matrix for analysis of the brain network using graph theory as well. For this reason, the Minimum Spanning Tree (MST) approach was selected to measure the graph parameters.

Minimum Spanning Tree

MST is a minimum-weight graph without any specific direction that connects all nodes without any cycles, while considering a minimum value for the total weight of edges (Mareš, 2008). Various algorithms have been introduced to construct the MST of a weighted graph including Kruskal, Prim, Reverse-Delete, and Boruvka's algorithms (Sedgewick and Wayne, 2011). In this study, Kruskal algorithm was utilized to obtain the MST. Kruskal algorithm ranks distances between all the nodes in an ascending order. Then, smallest possible tree is constructed by connecting pairs of nodes with the lowest-weight link between them. The procedure continues until all nodes are covered without any cycles (Kruskal, 1956; Prasad *et al*., 2014). In this study, six parameters of MST graph were used to investigate the brain network topology including degree, leaf number (L), betweenness (BC), eccentricity, diameter (D) and hierarchy (Th) (Boersma *et al*., 2013; Stam CJ *et al*., 2014). A leaf is defined as a node with only one link, and the longest distance in a tree is called Diameter. A node degree is defined as the number or summation of links that connect this node to others. The Betweenness of a node is the fraction of the number of shortest paths between all pairs of nodes that pass through this node to the total number of connections (0≤ BC≤1). The longest distance from one selected node to any other node is defined as eccentricity, and the maximum eccentricity in a graph is called the diameter. Tree Hierarchy, or an estimate of balance between diameter reduction and overload prevention (Vourkas *et al*., 2014), s defined as

$$Th = \frac{L}{2M * BC_{max}} \quad (4)$$

where BCmax is the maximum BC for all the nodes and M denotes the minimum number of links that connect all the nodes in the graph (N-1).

For further clarification, a simple tree is presented in Fig. 2 to illustrate the above mentioned six parameters. Three different topologies are presented consisting of N=9 nodes and M=8 edges. In the star topology (Fig. 2A), there is one central node which is connected to other nodes with only one edge. In this case, degree of central node is exactly equal to the number of edges (M=8) and the leaf number is (N-1=8) and diameter is 2. In contrast, several central nodes may be considered for other topologies (Fig. 2B,C) and a different degree could be calculated depending on the selected central node. As shown in Fig. 2, while moving from a star-like topology to a line-like topology, there is an increase in diameter and a decrease in leaf number. In addition, the maximum BC and hierarchy of a

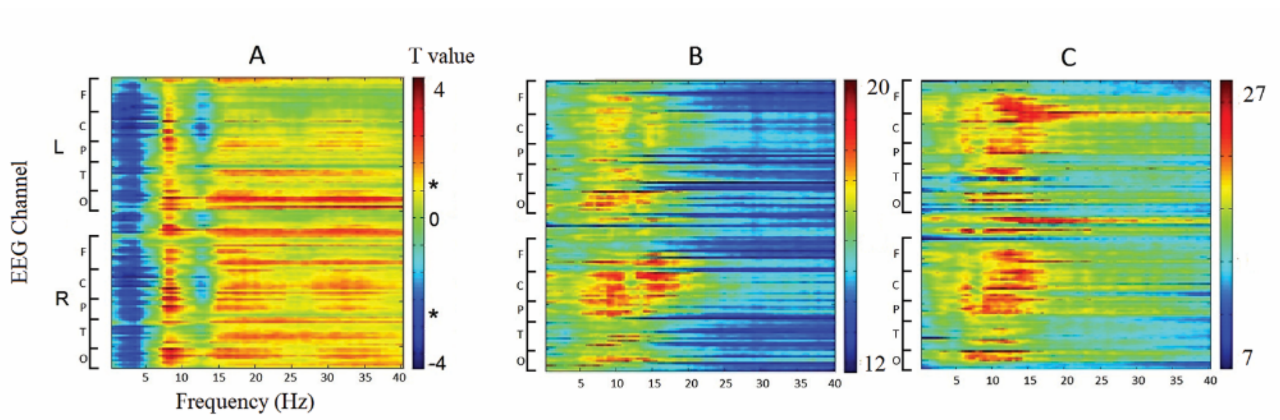

Figure 2. Schematic illustration of trees and tree measures. Circles show the nodes and lines are the edges of the trees.

star-like network (BC_{max}=1, Th=0.5) is higher than the line-like network (BC_{max}=0.5, Th=0.25). we have concluded that as the complexity of a graph declines, the leaf numbers decrease and the measure of degree will increase.

After calculation of the MST parameters, a statistical analysis is performed to recognize the significant changes in the brain functional network while growing from 6 to 18 month.

Statistical analysis

Extracted features including power spectrum and parameters of the brain functional network at the age of 6 months old were compared with those of 18 months old. Statistical analysis was performed using a paired t-test in Matlab. In our study, the power spectrum was calculated with a frequency resolution of 1 Hz, and for each frequency band comparisons were done separately. A threshold of $P<0.05$ corrected for family-wise error (Bonferroni method) (Abdi, 2007) was chosen to identify the significantly changed frequencies (Bland and Altman, 1995). Subsequently, the MST parameters were extracted from WPLI connectivity matrices of the selected frequency bands. A threshold of $P<0.05$ was chosen to identify significant changes in the network parameters.

Results and Discussion

Results

According to the results of power spectrum analysis, the frequency bands of [1-4], [7-10], [13-23], [30-40] Hz were selected. Fig. 3 presents the results. The WPLI was then calculated for the selected frequency bands and four band specific functional networks were estimated. The MST parameters of each network were then calculated, and statistical analysis was performed for each frequency band separately.

In the frequency range of 1-4 Hz, the result shows the leaf numbers and hierarchy have increased from 6 months to 18 months (significantly only in leaf numbers), while, eccentricity and diameter have decreased (Table 2). This finding demonstrates the topography of functional brain networks in the course of development has been changed almost similar to a shift from a line-like (Fig. 2C) to a star-like (Fig. 2A). The functional brain network in the higher frequency band [30-40 Hz] demonstrated a different behavior. In this band, there was significant increase in eccentricity and diameter, while leaf numbers, Betweenness, centrality and the hierarchy decreased. It can be observed that topography of functional brain networks in higher frequency band [30-40 Hz], through inverse trend of lower frequency

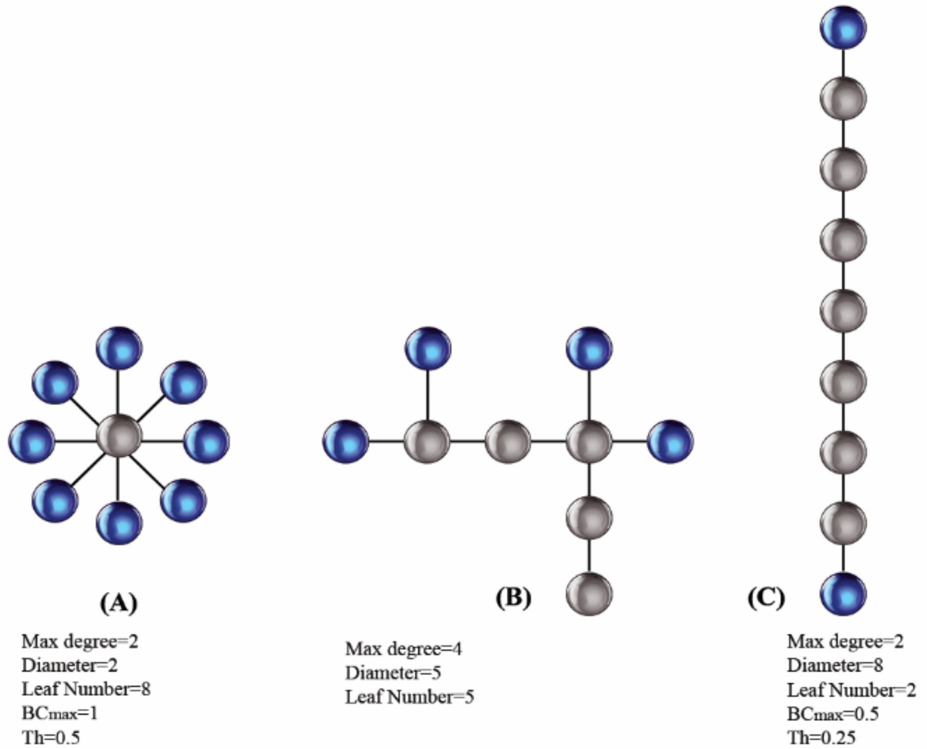

Figure 3. Developmental changes of oscillatory power. The colorbars denote t values of paired t-test performed between EEG data of 18-month and 6-month (A); Average power spectrum of 15 subjects (one sample t-test) at 6-month of the age (B), and 18-month of age (C). Abbreviations: F- Frontal, C- Central, P-Parietal, T-Temporal, O-Occipital, MID– Midline area, L- Left and R- Right. *: $P<0.05$, FWE corrected.

band, manifests itself in certain behavioral changes [1-4 Hz].

The results mainly illustrate that the changes in functional brain networks are frequency specific. Consequently, the effect of development is clearly observed in various frequency bands. It should be mentioned that brain functional networks in [7-10 Hz] and [13-23 Hz] did not present any significant changes.

To the topography of BC (average of all channels) at the ages of 6 months as well as 18 months, and developmental changes from 6 to 18 months presented in Fig. 4 clearly demonstrate this point.

Discussion

The MST method has been applied to test our hypothesis about the normal growth of brain networks during the developmental stage in early life of humans. In this study, functional brain networks and MST parameters were extrapolated from task-free EEG data. Therefore, the brain networks were investigated in a frequency specific manner. Our findings indicate that while growing up from 6 to 18 Months the organization of brain functional

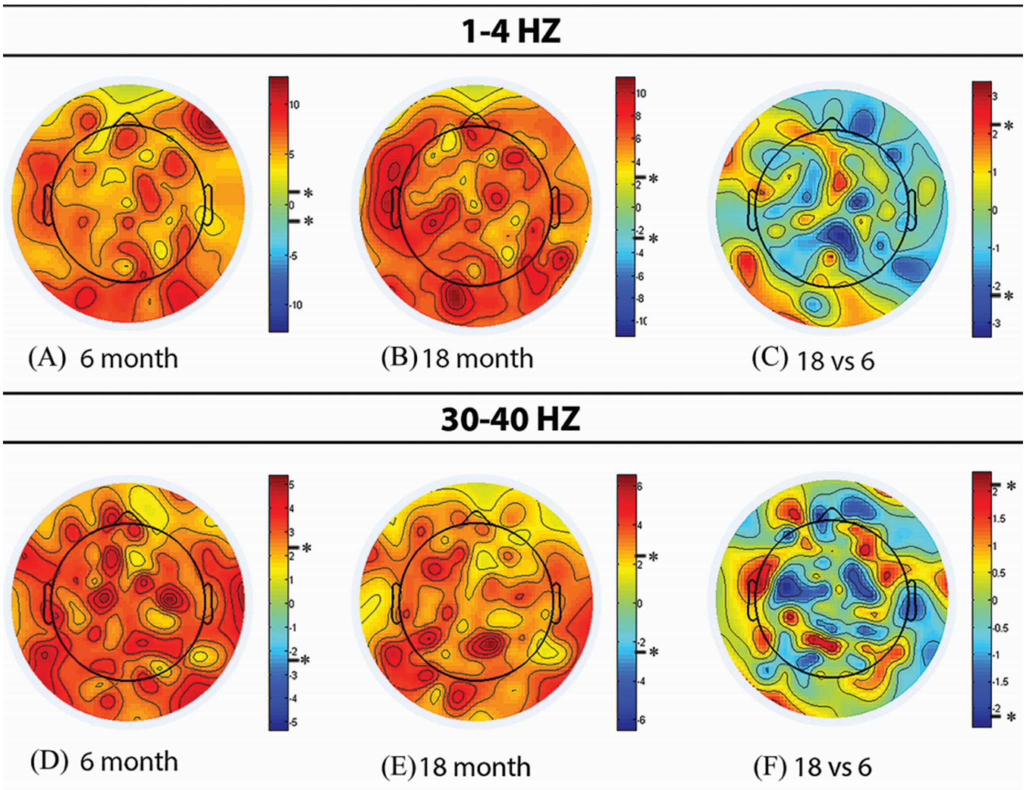

Figure 4. Developmental changes in Between topography. The colorbars denote t values of paired t-test performed between betweenness centrality at the 18-month and 6-month of the age (C, F); one sample t-test on betweenness centrality at the age of 6-month (A, D), and at the age of 18-month (B, E). * indicates P-value< 0.05.

Table 2. Developmental changes in parameters of the functional networks.

Frequency \ Parameters	Measures	Confidence interval		T-value	P-value
		Lower limit	Upper limit	18-month vs 6-month	
1-4 Hz	Leaf Number	0.0587	9.2747	2.1721	0.0475
	Eccentricity	-0.0467	0.0325	-0.3825	0.7078
	BC	-1.3827	0.5528	-0.9197	0.3733
	Diameter	-0.3296	0.1962	-0.5439	0.5950
	Hierarchy	-0.0467	0.0325	1.1869	0.2550
30-40 Hz	Leaf Number	-10.4871	5.6871	-0.6365	0.5347
	Eccentricity	-0.0001	0.0368	2.1322	0.0512
	BC	-2.7214	2.72387	-0.2088	0.8376
	Diameter	0.0045	0.0682	2.4495	0.0281
	Hierarchy	-0.0001	0.0368	-0.4629	0.6506

connectivity demonstrate significant changes in frequency bands of [1-4 Hz] and [30-40 Hz]. In the frequency band of [1-4 Hz], changes include a shift from a rather line-like decentralized organization (Fig. 2C) toward a star-like centralized network (Fig. 2A). Although, the power of lower frequency band [1-4 Hz] is decreased in the course of development, these findings clearly indicate that its related functional network becomes more complex as it loses its regularity.

According to the previous studies, changes in functional connectivity during a typical development are frequency and regionally specific. For instance, developmental changes of inter-hemispheric coherence in delta band are significant at the temporal region, but not at the frontal region of the brain. Hence, researchers believe a typical development is programmed in a way to increase or decline connectivity strengths in a regional-specific manner. In general, distant connections get stronger while local connections get weaker. In addition, decentralization of alpha band related functional connectivity has been indicated while growing from 5 to 7 years old (Boersma *et al.*, 2013). However, developmental re-organization of the brain vary in different frequency bands, and at various stages of the life. Based on this hypothesis, we speculate that development during the infancy period naturally programs the brain to shift from a line-like (de-centralized) form towards a star-like (centralized) network in the frequency range of 1 to 4 Hz.

On the other hand, the higher frequencies are emerged while growing up from 6 to 18 months. Therefore, a shift from a more random-like network towards a more regularized one in the frequency range of [30-40 Hz] should be expected. Our findings show development in higher frequencies involves a significant increase of eccentricity and diameter along with reduction of leaf numbers and the hierarchy of the network. These changes in MST parameters indicate that the brain functional organization shifts toward a more regulated network (a line-like network). Therefore, it is clearly observed that developmental changes in the early stage of life are due to a natural programming of the brain functional connectivity to become more centralized at lower frequencies, while getting more decentralized in higher frequencies.

It should be noted that there are a few limitations which could be investigated in the future studies. For instance, gender differences and an increase in the number of subjects might be worth consideration. In addition, behavioral and cognitive interrelations of these brain functional changes also might need to be investigated. Moreover, it would be interesting to look at the communication between these frequencies using cross-frequency coupling approach.

Conclusion and Outlook

Developmental changes in the brain functional topology can be investigated using graph theory. The MST method has proven to be superior to other existing graph theoretical approaches since it does not require establishing a threshold for the edges. The edge values were inferred through WPLI. We believe this is a more reliable approach than other connectivity measures. Therefore, in this study, developmental changes were tracked by MST parameters. Our findings demonstrate frequency specific changes which mainly are observed in the range of 1-4Hz and 30-40Hz. The developmental changes in these frequencies indicate that brain attains more centralized functional network at the lower frequencies, while its power declines in these frequencies. In contrast when higher frequencies emerge, it tries to decentralize its network.

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Author Disclosure Statement

This article is purely academic and it was written without any prejudice and without any conflict of interest.

Author Contributions

R.K designed and performed experiments, data analyses, and co-wrote the paper. P.S and F.J Performed experiments, data analyses and co-wrote the paper. R. K and HR. P Supervised the research.

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