Functional Network Development During the First Year: Relative Sequence and Socioeconomic Correlations

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The first postnatal year is characterized by the most dramatic functional network development of the human lifespan. Yet, the relative sequence of the maturation of different networks and the impact of socioeconomic status (SES) on their development during this critical period remains poorly characterized. Leveraging a large, normally developing infant sample with multiple longitudinal resting-state functional magnetic resonance imaging scans during the first year ($N = 65$, scanned every 3 months), we aimed to delineate the relative maturation sequence of 9 key brain functional networks and examine their SES correlations. Our results revealed a maturation sequence from primary sensorimotor/auditory to visual to attention/default-mode, and finally to executive control networks. Network-specific critical growth periods were also identified. Finally, marginally significant positive SES–brain correlations were observed at 6 months of age for both the sensorimotor and default-mode networks, indicating interesting SES effects on functional brain maturation. To the best of our knowledge, this is the first study delineating detailed longitudinal growth trajectories of all major functional networks during the first year of life and their SES correlations. Insights from this study not only improve our understanding of early brain development, but may also inform the critical periods for SES expression during infancy.

Keywords: first year, functional connectivity, functional networks, resting state

Introduction

The unique importance of the first year of life in human brain development is unquestionable. Converging evidence suggests that the most dramatic postnatal brain structural development occurs during the first year (Rakic et al. 1986; Andersen 2003; Knickmeyer et al. 2008; Petanjek et al. 2008; Gao, Lin, et al. 2009; Tau and Peterson 2010; Gilmore et al. 2012; Petanjek and Kostovic 2012). Consistently, remarkable behavioral milestones are also achieved during this period, including not only improved vision (Courage and Adams 1990) and body manipulation, but also a number of higher-order cognitive functions such as spatial attention (Haith et al. 1988; Johnson et al. 1991), working memory (Diamond and Goldman-Rakic 1989; Reznick et al. 2004; Reznick 2007), and self-awareness (Amsterdam 1972). However, the intermediate agent between brain structure and behavior, the brain's functional circuits, received little attention in previous studies, which is likely due to the lack of appropriate noninvasive imaging techniques suitable for assessing the infant brain.

The resting-state functional magnetic resonance imaging (rsfMRI) technique (Biswal et al. 1995) provides a compelling means to probe the brain's functional organization during infancy. Several studies (Smyser et al. 2010; Doria et al. 2011) have consistently shown the prenatal development of functional connectivity resulting in qualitatively adult-like sensorimotor, auditory, and visual networks in neonates (Fransson et al. 2007, 2010; Lin et al. 2008; Gao et al. 2014). Postnatally, our own data have consistently revealed a nonlinear growth trend of different functional systems, including the default-mode (Gao et al. 2009) and dorsal attention networks (Gao et al. 2012), as well as for whole brain efficiency (Gao et al. 2011), featuring the most dramatic improvements during the first year of life. Consistently, Damaraju et al. (2013) imaged normal pediatric subjects at 4 and 9 months and showed decreased local functional connectivity and increased distant connectivity, exemplifying the dynamic functional maturation process during this critical period. However, the development of functional connectivity during the first year of life is also most likely nonlinear. Without a longitudinal design and multiple (>2) imaging time points within this period, it would be impossible to delineate such nonlinear growth trends and their relative sequence which are essential for the identification of network-specific critical growth periods with maximum growth rates.

In this study, leveraging a large sample of normally developing infants ($N = 65$) with multiple longitudinal rsfMRI scans (every 3 months), we aimed to delineate detailed growth trajectories of 9 key functional brain networks (Smith et al. 2009) during the first year of brain development. The potential relationship between socioeconomic status (SES) and brain functional network development was also studied. Given previous findings, we hypothesized a maturation sequence beginning with primary networks, then attention and self-awareness-related networks, and finally, networks governing executive functions (Changeux and Danchin 1976; Huttenlocher and Dabholkar 1997a; Rothbart and Posner 2001; Elston et al. 2009; Tau and Peterson 2010; Petanjek et al. 2011). We also expected significant correlations between SES parameters and network connectivity measures during this critical brain developmental period. Insights gained from this study will, for the first time, provide a comprehensive picture of the normative growth trends of 9 key brain functional networks during the entire first year of life and potentially inform the importance of SES factors in normal brain development during this time period.

Materials and Methods

Subjects

A large sample of normal developing infants ($N = 65$, 35 females) with multiple longitudinal rsfMRI scans (every 3 months, starting from <1 month ($N = 45$), 3 months ($N = 34$), 6 months ($N = 33$), 9 months ($N = 29$) to 12 months ($N = 35$), total number of scans = 176) during the first year of life was retrospectively identified for inclusion in this

study. Inclusion criteria were birth between gestational age of 35 and 42 weeks, appropriate weight for gestational age and the absence of major pregnancy and delivery complications as defined in the exclusion criteria. Exclusion criteria included: maternal pre-eclampsia, placental abruption, neonatal hypoxia, any neonatal illness requiring greater than a 1-day stay at neonatal intensive care unit, maternal HIV infection, maternal drug or narcotic use during pregnancy, any chromosomal or major congenital abnormality, and severe motion artifacts requiring removal of over one-third of rsfMRI volumes (detailed in the "Preprocessing" section). Before imaging, subjects were fed, swaddled, and fitted with ear protection. All subjects were imaged in a natural sleep state. A board-certified neuroradiologist (J.K.S.) reviewed all images to verify that there were no clinically relevant abnormalities. The distribution of gestational ages at which the included subjects had available rsfMRI scans is shown in Figure 1. The socioeconomic information about the parents of the included subjects is provided in Table 1. Besides pediatric subjects, normal adult subjects ($N = 19$, age 27–40, 5 females) (Gao et al. 2013; Elton and Gao 2014) were also included in this study to provide reference networks for comparison with the pediatric subjects. Informed consent was obtained from parents of each infant subject and from each adult participant. The
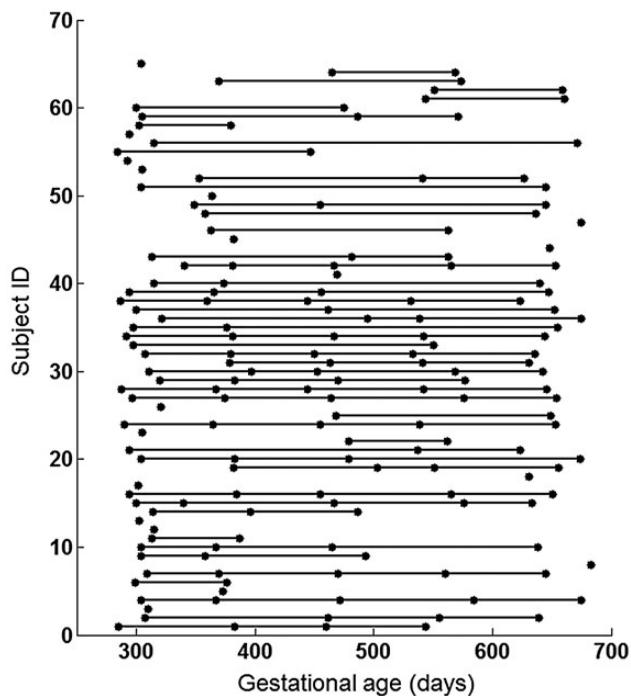

Figure 1. The distribution of gestational ages for all included pediatric subjects whose image quality passed the quality control procedures. Each dot represents one successful rsfMRI scan from one subject and dots along each line represent all available longitudinal scans of a subject.

experimental protocols were approved by the biomedical institutional review board of UNC-Chapel Hill.

Imaging

All images were acquired using a 3-T MR scanner (Siemens Medical Systems, Erlangen, Germany) housed in the Biomedical Research Imaging Center (BRIC). rsfMRI was acquired using a T_2*-weighted EPI sequence: time repetition (TR) = 2 s, time echo (TE) = 32 ms, 33 slices, voxel size of $4 \times 4 \times 4$ mm³. One hundred and fifty volumes were acquired in 5 min. In order to provide anatomical reference, structural images were acquired using a 3D Magnetization Prepared Rapid Acquisition Gradient-Recalled Echo sequence (TR = 1820 ms, TE = 4.38 ms, inversion time = 1100 ms), with a voxel size of $1 \times 1 \times 1$ mm³.

Preprocessing

Functional data were preprocessed using FMRIB's Software Libraries (FSL, v 4.1.9) (Smith et al. 2004). The preprocessing steps included discarding the first 10 volumes, slice timing correction, motion correction, high-pass (>0.01 Hz) and low-pass filtering (<0.08 Hz). Mean signal from white matter, cerebrospinal fluid, whole brain, and 6 motion parameters were removed using linear regression. Adaptive spatial smoothing was performed with different Gaussian kernels (Full width at Half Maximum of 4, 4.9, 6.3, 7.0, and 8.2 mm for the 1-, 3-, 6-, 9-, and 12-month scans, respectively, calculated based on the relative ratio of different brain sizes across the 5 age groups) to minimize the effect of different brain sizes in connectivity measurement. Results without applying the above outlined adaptive smoothing (i.e., no spatial smoothing) were also obtained for comparison. In order to further reduce the effect of motion on functional connectivity measures, the "scrubbing" approach of controlling the global measure of signal change (0.5%) and frame-wise displacement (0.5 mm) was carried out as proposed by Power et al. (2012). Subjects with more than one-third of volumes (i.e., 50 volumes) removed from the scrubbing procedure were excluded from subsequent analyses. Note the 2 motion parameters: (1) Volumes removed during the "scrubbing" process for each subject and (2) the residual frame-wise displacement (FD) measurement after the scrubbing process, together with 2 subject variables: gestational age and sex, were included as covariates of no interest in all subsequent statistical comparisons, longitudinal growth modeling, and SES connectivity correlations, to control for these confounding factors in our developmental analysis. For each subject and session, after an initial rigid alignment between functional data and the T_1 high-resolution structural images, a nonlinear transformation field was obtained from the individual T_1 images to a longitudinal T_1-template, that is, T_1 images of a subject scanned at the same 5 time points during the first year, using FSL (Smith et al. 2004; Gao et al. 2010; Alcauter et al. 2015). The combined transformation field was used to warp the preprocessed rsfMRI data to the template. Identical postprocessing procedures were also applied to the 19 adult subjects (Gao et al. 2013; Elton and Gao 2014).

Network Analysis

Seed-based functional connectivity analyses were conducted to define 9 functional networks discerned by Smith et al. (2009). Specifically, 9 adult functional neural networks, including the medial occipital

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Table 1

Socioeconomic status and demographic information about parents whose offspring were included in this study

	Paternal age (years)	Paternal education (years)	Maternal age (years)	Maternal education (years)	Total income (10^4 dollars)	*SES scores
Mean and standard deviation	31.080 ± 6.675	15.426 ± 4.014	27.846 ± 5.191	15.500 ± 3.375	5.926 ± 4.453	39.654 ± 14.380
Range	20–46	9–27 (ninth grade Doctorate degree)	18–41	9–22	0–18.5	14–66

Note: Occupation scores range from 1 to 9 and are based on the following categories: 1, farm labor/menial service work; 2, unskilled work; 3, machine operation/semiskilled work; 4, small business/skilled manual work; 5, clerical/sales work; 6, semiprofessional work/technical work; 7, management/minor professional work; 8, administration/lesser professional work/small business owner; 9, higher executive work/major professional work/large business owner.

Education scores range from 1 to 7 and are based on the following categories: 1, <7th grade completed; 2, 8–9th grade completed; 3, 10–11th grade completed; 4, high school completed; 5, partial bachelors/associates degree completed; 6, Bachelor degree completed; 7, >16 years of education completed.

*Socioeconomic scores are calculated using the Hollingshead Four-Factor Index of SES (Hollingshead 1975), which has a parental combined range of 8–66. Score are based of parental occupation and years of parental education. Socioeconomic scores for each parent are found by multiplying the parental occupation score by 5, multiplying the years of parental education score by 3, and summing the scores together. For 2 parent household, the mean of parental socioeconomic scores is used; for single parent households, the socioeconomic score of the single parent is used.

network (V1), the occipital pole network (V2), the lateral visual/parietal network (V3), the default-mode network (DMN; Raichle et al. 2001), the sensorimotor network (SM), the auditory/language network (AN), the salience network (SA), and the two lateralized frontoparietal networks (FPNs) were selected. A sphere with 8-mm radius, centered at the global maximum of each network map (provided by Smith et al. 2009), was defined as the seed point for a whole-brain Pearson correlation analysis to define the corresponding network at each age. Specifically, seeds were located in the right precentral gyrus, left superior temporal gyrus, calcarine cortex, occipital pole, right lateral occipital cortex, posterior cingulate cortex (PCC), anterior cingulate cortex, and bilateral inferior parietal lobule (IPL) for SM, AN, V1, V2, V3, DMN, SA, and bilateral FPNs, respectively. Subsequently, all seeds were warped to the age-specific template using 4D HAMMER registration (Shen and Davatzikos 2002, 2004) to calculate the corresponding functional connectivity maps at each age point. The same seeds were also applied to the rsfMRI data of the 19 adult subjects (Gao et al. 2013) to obtain the corresponding matured functional networks for subsequent quantitative comparisons with those obtained from our pediatric subjects. All resulting functional connectivity maps from the pediatric subjects were warped to the adult MNI template using 4D HAMMER registration (Shen and Davatzikos 2002, 2004) for subsequent statistical comparison and modeling. Two-tailed *t*-tests were performed to detect significant connections ($P < 0.05$ after FDR correction Benjamini and Yekutieli, 2001) for each network and each age group. Moreover, to delineate the temporal changes of functional network topologies, two-sample *t*-tests were performed on the individual functional connectivity maps of each network across any 3-month period (i.e., between 0 and 3 months, 3 and 6 months, 6 and 9 months, 9 and 12 months) as well as between 0 and 6 months, 6 and 12 months, and between 0 and 12 months. Brain areas that showed a significant increase or decrease in functional connectivity within a given network were detected using a significance threshold of $P < 0.05$ after FDR correction.

To delineate longitudinal growth trajectories of different functional networks, 3 quantitative measures characterizing the within-network connectivity, outside-network connectivity, and overall similarity to the adult references were defined. Specifically, using the adult group-level significant functional networks as references, a binary mask was derived for each network. Subsequently, the within-network connectivity was defined as the mean functional connectivity strength within the mask, indicating the degree of within-network synchronization, whereas outside-network connectivity was the mean functional connectivity of areas outside the network mask (but showing non-negative functional connectivity in the corresponding adult reference map), indicating the degree of outside-network specialization. Finally, based on a previously established network matching concept (Greicius et al. 2004), the subtraction of the outside-network connectivity from within-network connectivity yields a network matching score, indicating the degree of similarity between the network in question and the adult reference network in terms of functional connectivity strength distribution of the whole brain. This network matching score was used as an overall measure quantifying the maturation of individual networks in this study.

A linear mixed-effect regression (LMER) model (Verbeke and Molenberghs 2000) was used to delineate the longitudinal network growth curves. An LMER model was selected (implemented in R) owing to its ability to handle missing data (Fig. 1) in longitudinal settings. Moreover, the fact that age could be modeled as a continuous variable in LMER is essential since infant subjects were not scanned at the exact same gestational age for the 5 time points. Specifically, each of the 3 network maturation measures (i.e., within-network connectivity, outside-network connectivity, and network matching score) was modeled as a dependent variable, and age or log(age) and sex were entered as independent variables. Random intercept and age effects were included to characterize temporal correlation. The Akaike information criterion (AIC) was used for model selection between age and log(age) fit. To further compare the growth rates of different functional networks, we took the differences of each of the 3 measures between any 2 functional networks and the differences were similarly modeled in the LMER model with age and sex as independent variables (plus random effects on intercept and age effects). A significant age effect in this difference-LMER model would indicate significant differences in growth rates between 2 given networks.

For all models, significance was defined as $P < 0.05$ after FDR correction. As mentioned above, volumes removed during the "scrubbing" process for each subject, the residual FD measurement after the scrubbing process, gestational age and sex were included as covariates of no interest in both the across-age statistical comparisons and the longitudinal growth modeling process to control for these confounding factors.

Finally, the potential effects of SES parameters on both the longitudinal growth trajectories and cross-sectional network measures were tested. For their effects on longitudinal growth trajectories, each of the 3 interaction terms [i.e., income*age/log(age), years of maternal education (YME)*age/log(age), years of paternal education (YDE)*age/log (age)] was added one at a time as an independent variable to the above-described LMER models to quantify the individual growth trajectories and tested separately to test for a significant interaction effect. For cross-sectional effects, the partial correlation between each SES parameter and each of the three network measures for each network at each age was calculated after controlling for the effects of 4 covariates (i.e., volumes removed during the "scrubbing" process for each subject, the residual FD measurement after the scrubbing process, gestational age, and sex). Significance was defined as $P < 0.05$ after FDR correction. To validate our findings, bootstrapping of the observed correlations showing a $P < 0.05$ was performed based on 1000 times resampling with replacement, and the 95% bootstrap confidence interval was calculated for each correlation.

Results

Development of Functional Connectivity Maps

The functional connectivity maps of the 9 functional networks evaluated at 5 time points during the first year are shown in Figure 2. Specifically, the SM and AN together with the 2 primary visual networks (i.e., V1 and V2) already demonstrate bilateral symmetric topology at birth, resembling their adult topology. These networks also exhibit minimal topological changes during the first year. Therefore, these 4 networks seem to represent the earliest developing functional networks. In contrast, the other 5 higher-order networks demonstrate either local diffusive blobs (i.e., DMN, SA) or primitive bilateral symmetric connectivity (i.e., V3, bilateral FPNs) in neonates that barely resembles their respective adult topologies. Nevertheless, the lateral visual/parietal network (V3) and the DMN, although not adult-like in neonates, demonstrate substantial age-dependent increases in connectivity with spatially distributed functional areas [i.e., superior parietal lobule (SPL) regions for V3; orbital frontal cortex (OFC), medial prefrontal cortex (MPFC), bilateral hippocampus/parahippocampal regions (HP), lateral temporal cortex (LTC), and inferior parietal lobule (IPL) for DMN] during the first year of life, leading to adult-like topology for both networks in 1 year old. Therefore, V3 and DMN networks seem to follow the primary networks and form an intermediate group in terms of development. However, the SA and bilateral FPNs show only moderate improvements in network topologies during the first year of life, leading to still premature network topologies at the end of the first year. Therefore, the SA and the FPN represent the latest developing networks. Results without spatial smoothing (Supplementary Fig. 1) are highly consistent with those in Figure 2.

Fastest Growth Period(s)

To better characterize the fastest growth period for each network, quantitative comparisons of the functional connectivity strength between 6 month olds and neonates, between 12- and 6 month olds, and between 12 month olds and neonates are presented in Figure 3*A*,*B*, while more detailed comparisons
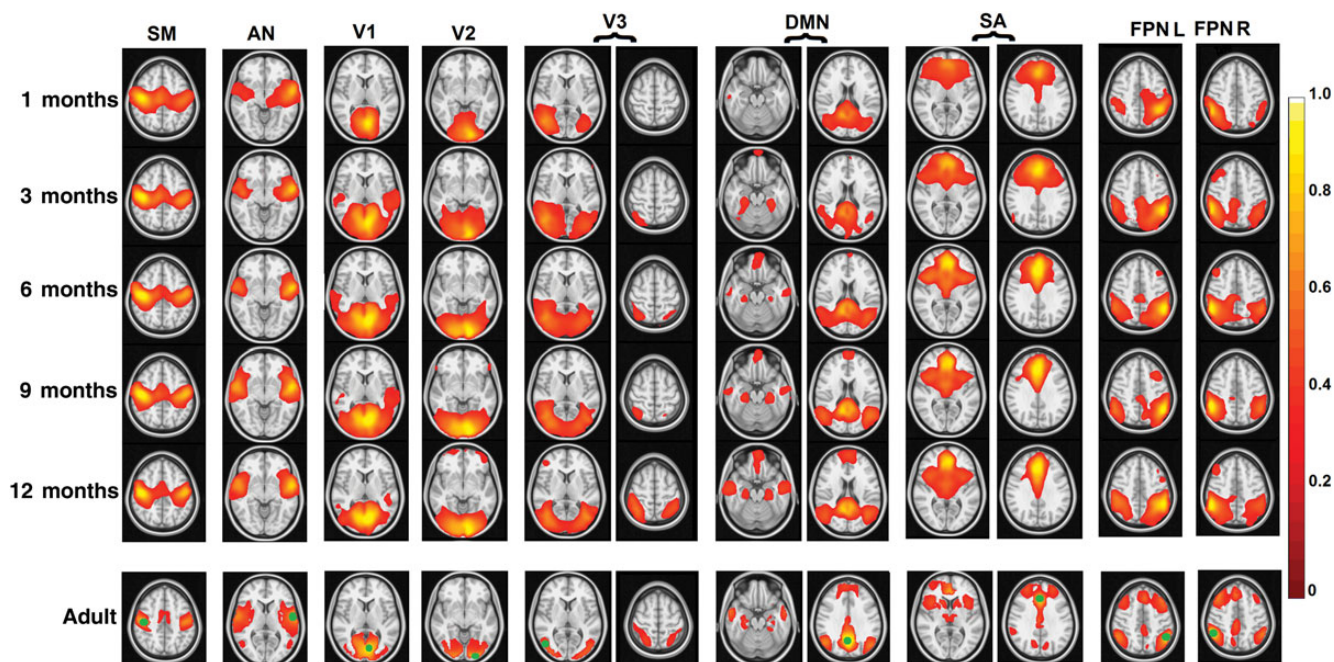
Figure 2. Development of the 9 brain cortical functional networks. Thresholded maps ($P < 0.05$ after FDR correction) evaluated at each of the 5 time points were shown from the first to the fifth rows and the corresponding adult maps were shown at the bottom row (green dots show the locations of seeds). Color bar indicates correlation strength. The images are in radiological convention (the right side of the brain is on the left side of image).

across every 3-month span are shown in Figure 3C. It is immediately apparent that major changes occur during the first half year for all networks (except for SM and AN) while changes in the second half of the year were not uniform. More importantly, such quantitative comparisons further differentiate V1 and V2 from SM and AN in their development sequences; V1 and V2 show dramatically enhancing synchronization within medial and occipital pole regions, respectively (particularly during the first 3 months, Fig. 3A,C), while SM and AN demonstrate stable connectivity with only minor changes throughout the first year. This finding suggests that SM and AN likely achieve a matured network configuration both qualitatively (Fig. 2) and quantitatively (Fig. 3) at birth, while V1 and V2 experience further quantitative strengthening postnatally (Fig. 3). Therefore, V1 and V2 should follow SM and AN in their developmental sequence. For V3 and DMN, focused increases in connectivity strength within core network areas (e. g., bilateral LOC and SPL for V3 and OFC, MPFC, HP, LTC, and IPL for DMN) are consistently observed across the two halves of the first year with differential spatial emphases, indicating continued development across the entire year. For the SA and bilateral FPNs, dramatic increases in functional connectivity strength among core network areas are also observed across the first two halves of the first year, despite minimal topological improvement as shown in Figure 2. For all networks, significant decreases within mostly outside-network regions are observed indicating a general within-network synchronization and outside-network specialization trend. More detailed 3-month comparisons (Fig. 3C) seem to suffer from relatively subtle changes to detect significance, but highlight that the most dramatic changes occur during the first 3 months of life for V1, V2, DMN, SA, and bilateral FPNs. FPN L seemed to show another fast-developing period between 9 and 12 months (Fig. 3C).

Longitudinal Growth Trajectories

The longitudinal growth trajectories of the network matching score are shown in Figure 4. Consistent with the patterns observed in Figures 2 and 3, the SM and AN networks demonstrate non-significant changes in the network matching score, but V1, V2, V3, DMN, SA, FPN L, and FPN R all show significant log-linear increases in the network matching score (Fig. 4A). Overall, the orders of network growth rates from fastest to slowest for both network matching score and within-network connectivity are consistent: V1 > V2 > V3 > DMN > SA > FPN L > FPN R > AN > SM (Fig. 4B and Supplementary Fig. 2). Statistically, the medial occipital network, V1, demonstrates the fastest growth rates in both network matching score and within-network connectivity when compared with all the other 8 functional networks ($P < 1e-6$). Subsequently, the V2, V3, DMN, SA, and FPN L show faster growth in both network matching score and within-network connectivity than FPNR, AN, and SM ($P < 0.001$). In terms of the outside-network connectivity, the only significant differences are between SM, AN and FPN L, whereas SM and AN show faster decreases than FPN L ($P < 0.001$). The longitudinal growth trends of within-network and outside-network connectivity shown in Supplementary Figure 2 indicate that the significant increases of network matching score in V1, V2, V3, DMN, SA, and bilateral FPNs are driven by increases in within-network synchronization. In contrast, SM and AN are characterized by non-significant decreases of within-network, but significant decreases of outside-network functional, connectivity.

Overall, through both qualitative evaluation of the functional connectivity maps and quantitative examination of the growth rates during the first year of life, our results suggest a tentative grouping of the 9 functional networks according to their relative timing of development from the earliest to the
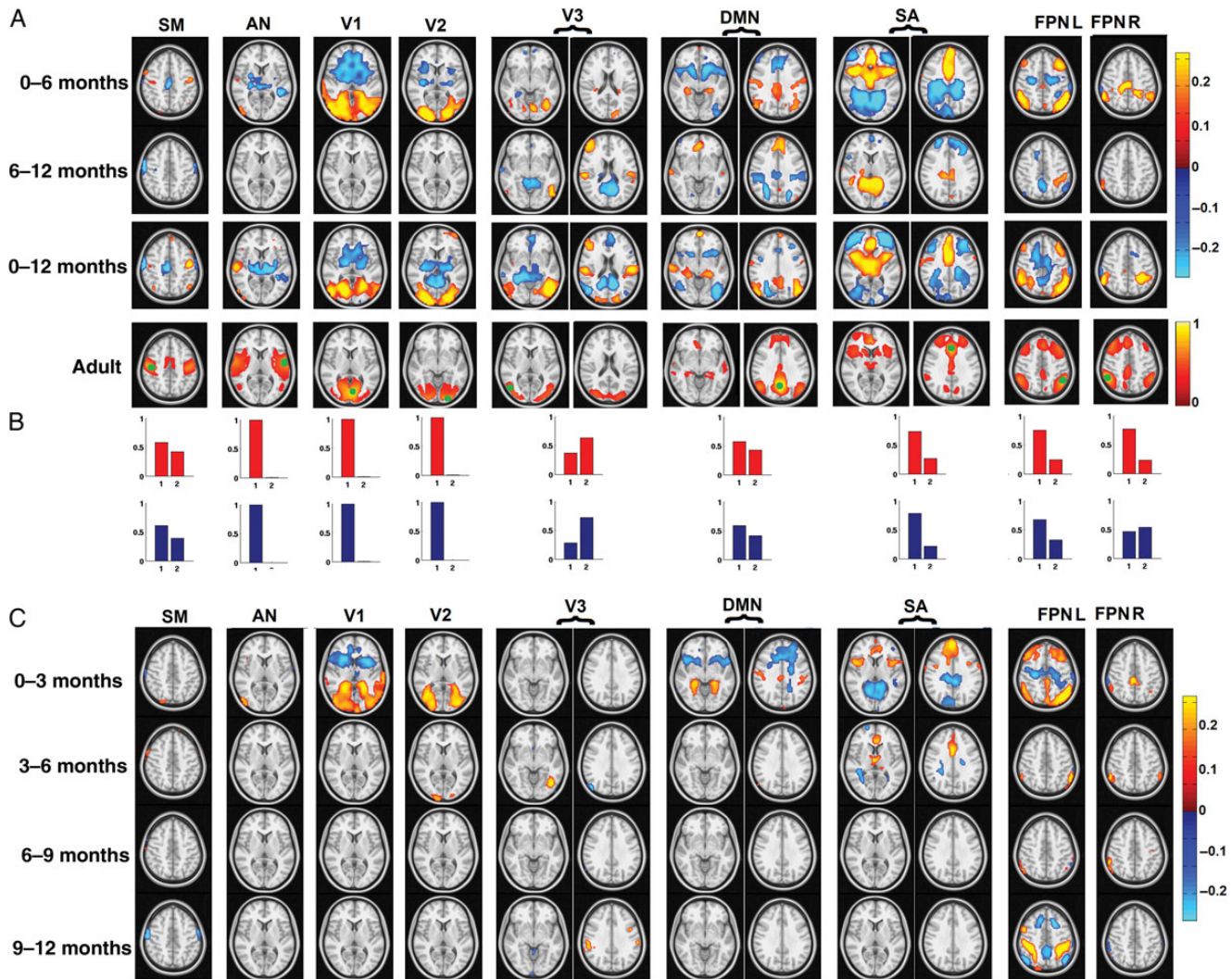
Figure 3. Detailed development trends of the 9 functional networks during the first year of life. (*A*) The comparisons between 6 months and neonates, 12 and 6 months, 12 months and neonates are shown from the first to the third rows, respectively. The adult functional network structures are presented in the bottom row for comparisons. (*B*) Comparisons of the amount of significant changes between 0 and 6 months (labeled as 1) and 6 and 12 months (labeled as 2) are shown. Top row: Percentages of voxels showing a significant increase in functional connectivity for all networks (normalized against the number of voxels showing a significant increase during the whole year). Bottom row: Percentages of voxels showing a significant decrease in functional connectivity for all networks (normalized against the number of voxels showing a significant decrease during the whole year). (*C*) More detailed development trends of 9 functional networks during the first year of life. The comparisons across every 3-month periods are shown from the first to the fourth row, respectively. The images are in radiological convention (the right side of the brain is on the left side of image).

latest: SM/AN->V1/V2->V3/DMN->SA/bilateral FPNs. Table 2 summarizes the corresponding developmental characteristics associated with each group of networks.

Socioeconomic Status Correlations

Finally, the correlations between SES and functional network development are shown in Figure 5. Although none of the correlations survive multiple corrections, marginally significant correlations were detected between 2 SES parameters (i.e., income and YME) and functional connectivity measures of the DMN and SM networks at 6 months of age ($P < 0.005$). Specifically, higher income corresponded with both higher network matching scores ($R = 0.57$, $P = 0.0013$, bootstrapping confidence interval for R: [0.30, 0.77]) and higher within-network connectivity ($R = 0.51$, $P = 0.0044$, bootstrapping confidence interval for R: [0.23, 0.71]). Similarly, higher maternal education was related to both higher network matching scores ($R = 0.47$, $P = 0.0098$, bootstrapping confidence interval for

R: [0.20, 0.69]) and within-network connectivity ($R = 0.50$, $P = 0.0053$, bootstrapping confidence interval for R: [0.25, 0.72]) at 6 months of age for the SM. In contrast, higher income was associated with lower outside-network connectivity (outside-network connectivity) for the DMN at the same age ($R = -0.50$, $P = 0.0057$, bootstrapping confidence interval for R: [-0.69, -0.21]). No significant effects were detected at any other age points. Additionally, there were also no significant effects detected for the interaction between SES parameters and longitudinal growth rates of any network.

Discussion

This study delineated the growth trends of 9 functional networks during the first year of life. Overall, a maturation sequence starting with primary sensorimotor/auditory, vision, then attention/default-mode networks, and finally, executive control networks was observed together with network-specific critical periods of
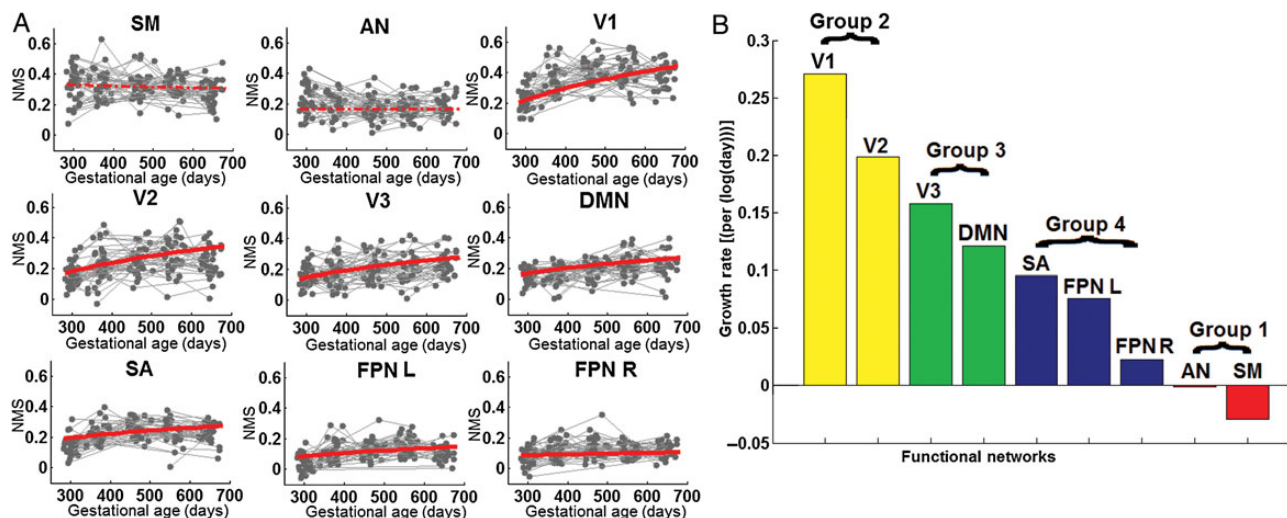
Figure 4. Longitudinal growth trajectory of the network matching scores (NMS) for each functional network. (*A*) NMS growth curves. Bold red lines indicate the group trend while the underlying gray lines are spaghetti plots representing curves from individual subjects. Significant age-dependent group-level growths (log-linear, *P* < 0.05, FDR corrected) are shown in solid lines, whereas non-significant ones are in dashed lines. (*B*) Bar plots of the growth rates [per log(day)] from different functional networks. The groupings of different groups are based on Table 2.

Table 2
Developmental characteristics of different groups of networks

Networks in developmental order	Qualitative network topology at birth	Fastest growth period	Overall growth rate [per log (day)]	Qualitative network topology at 1 year	Overall developmental ranking
Primary networks					
SM, AN	Adult-like	Not identified	SM: −0.029 AN: −0.00095	Adult-like	Earliest
V1, V2	Adult-like	0–3 months	V1: 0.271 V2: 0.199	Adult-like	Second
Higher-order networks					
V3, DMN	Premature	0–12 months	V3: 0.158 DMN: 0.121	Adult-like	Third
SA, bilateral FPNs	Premature	0–3 months (plus 9–12 months for FPN L)	SA: 0.095 FPN L: 0.076 FPN R: 0.023	Premature	Latest

V1, medial occipital network; V2, occipital pole network; V3, lateral visual/parietal network; DMN, default-mode network; SM, sensorimotor network; AN, auditory/language network; SA, salience network; FPNs: frontoparietal networks.

growth. Moreover, SES parameters including income and YME showed significant correlations with different network maturation measures of the default-mode network and SM at 6 months of age.

The dramatic maturation of different functional networks during the first year of life is not surprising given mounting evidence on fast synaptogenesis (Rakic et al. 1986; Elston et al. 2009), dendrite elaboration (Petanjek et al. 2008), myelination (Flechsig 1901; Gao, Lin, et al. 2009), white matter fiber tract development (Huang et al. 2006; Yap et al. 2011), and continued subplate growth (Kostovic et al. 2014). However, the differential growth patterns of different brain functional networks reported here are intriguing and convey exciting new information regarding the relative developmental sequence of different networks which might offer valuable insights into our

understanding of early brain functional development. Specifically, given the observed patterns, the 9 functional networks could be potentially characterized into 4 groups (Table 2), likely indicating a maturation sequence from the earliest to the latest: SM/AN->V1/V2->V3/DMN->SA/bilateral FPNs, which will be discussed in detail below.

Adult-Like Networks at Birth with Minimal Changes During the First Year

The SM and AN networks seem to be the earliest developing networks with their within-network synchronization largely established before birth. This finding is a replicate of several previous reports showing the bilateral symmetric, adult-like topology of both networks at birth (Lin et al. 2008; Gao et al. 2014) or even prenatally (Smyser et al. 2010; Doria et al. 2011), indicating significant prenatal development of these 2 networks. These convergent findings are highly consistent with the documented capability of fetuses in voluntary movement (Kisilevsky and Hains 2005), sensory processing (Bartocci et al. 2006; Lagercrantz and Changeux 2010), and auditory stimuli response (Hykin et al. 1999). Therefore, existing evidence strongly suggests the earliest maturation of these 2 primary networks. In this study, we further showed a slight trend of specialization (decreases) of connectivity strength of both networks (Supplementary Fig. 2) during postnatal development, which may be related to early pruning of synapses within sensory-related areas (Huttenlocher 1990; Huttenlocher and Dabholkar 1997b).

Adult-Like Networks at Birth with Continued Maturation During the First Year

Similar to SM and AN, V1 and V2 show an adult-like spatial topology in neonates (Fig. 2), suggesting an early maturation, which is consistent with the visual processing capability in neonates (Born et al. 1996). However, unlike the SM and AN, which exhibited rather stable connectivity during year 1 (Fig. 4A, non-significant changes in network matching score during the first year), continued quantitative improvement of
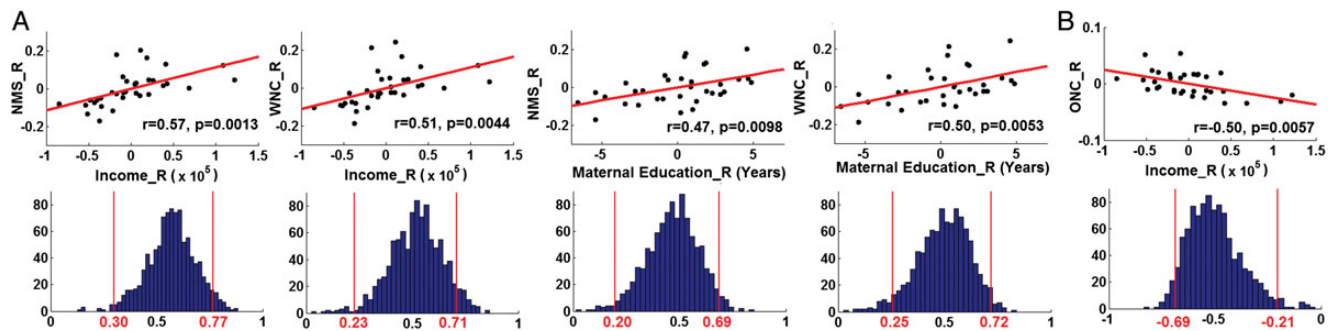
Figure 5. SES correlations with network functional connectivity measures. (*A*) The relationship between income and network matching score (NMS) of the SM network (first panel); income and within-network functional connectivity (WNC) of the SM network (second panel); maternal education and network matching score of the SM network (third panel), maternal education and within-network connectivity of the SM network (fourth panel) at 6 months of age. (*B*) The relationship between maternal education and DMN network outside-network connectivity (ONC) at 6 months of age. Note the residual values of both SES parameters and functional connectivity measures after regressing out the covariates of no-interest (see Materials and Methods section, indicated by _R) are plotted to visualize their partial correlations. Black dots represent individual subjects and red lines are the fitted regression lines to show the linear trend. The histograms of correlations based on 1000 times bootstrapping were visualized below each correlation scatter plot with red vertical lines, indicating the confidence intervals of each correlation estimate.

both within-network connectivity and network matching score is observed for V1 and V2 (Figs 3 and 4, and Supplementary Fig. 2). In fact, V1 and V2 show the fastest growth rates (Fig. 4*B*) with the most significant increase between 0 and 3 months (Fig. 3*C*). These findings are consistent with the improved acuity of visual perception during the first few months of life (Courage and Adams 1990) and the gradual establishment of visual pathways in year 1 (Johnson 1990; Dubois et al. 2008). Overall, findings in this study suggest that V1 and V2 are the second earliest developing functional networks following SM and AN since they show adult-like topology in neonates and most of the quantitative connectivity increases occur during the first 3 months of life (Fig. 3*C*).

Networks Far From Adult-Like at Birth but Showing Substantial Growth to Become Adult-Like at 1 Year of Age

The third group of networks consists of the V3 and DMN. They exhibit limited and far-from-mature synchronization at birth, but experience significant age-dependent growth of both qualitative topology and quantitative connection strength during the first year, becoming adult-like at the end of year 1 (Figs 2–4). More specifically, V3 demonstrates improved synchronization between bilateral lateral occipital cortex and distant parietal/frontal regions during the first and second half of the first year, respectively (Fig. 3*A*). For DMN, the first 6 months are characterized by increased connectivity with areas of bilateral HP, IPL, and PCC, whereas the second 6-month feature significant synchronization with the distant MPFC and bilateral LTC (Fig. 3*A*). Therefore, in contrast to V1 and V2 which show the most development during the first 3 months, V3 and DM demonstrate continuous improvement throughout the first year and, more importantly, with age-dependent focuses. The V3, encompassing bilateral lateral occipital and superior parietal regions in its adult topology, resembles the dorsal attention network (Corbetta and Shulman 2002; Fox et al. 2005). Therefore, findings in this study are highly consistent with our previous reports (Gao et al. 2009; Gao et al. 2012) regarding the significant growth of both dorsal attention and DMNs during the first year which also echo behavioral improvement in spatial attention (Haith et al. 1988) and self-awareness (Amsterdam 1972). Nevertheless, results from this study revealed new insights into the age-specific focuses of network

synchronization for both networks (Fig. 3*A*) during the first year. Particularly, robust long-distance synchronization between the 2 typical hubs of the DMN (i.e., MPFC and PCC) was observed to show dramatic strengthening and become established during the second half of the first year (although PCC–OFC synchronization seems to be established earlier, Figs 2 and 3*A*), providing new and vital details on the development of this important functional network (Gao et al. 2009). Overall, the dramatic improvement of network topology observed for both V3 and DMN and the fact that they achieve adult-like structures at the end of the first year put these 2 networks behind V1 and V2, forming the third earliest group of networks in terms of development.

Networks Far From Adult-Like at Birth with Minimal Improvements During the First Year

Finally, similar to the V3 and DMN, the SA and bilateral FPNs demonstrate limited and far-from-mature synchronization structures in neonates. However, different from the V3 and DMN, the SA and bilateral FPNs show limited improvement in their network topology and are still far from adult-like at the end of the first year. Specifically, although both networks show statistically significant increases in within-network connectivity (Figs 3 and 4), their growth rates are the slowest among all networks showing positive growth rates (Fig. 4*B*), resulting in minimal changes in the qualitative topology at the end of the first year (Fig. 2). Compared with the adult topology of SA, the pediatric SA is consistently characterized by a large blob showing moderate topological specializations with age. Interestingly, in our previous studies (Alcauter et al. 2015), we have observed more distributed connectivity of the SA network at 1-year of age based on a much larger sample size ($n = 143$), suggesting that the non-significance of remote connectivity in SA observed in this study could be partially driven by the relatively small sample size. However, the fact that networks in the third group (i.e., V3 and DMN) show robust long-range connectivity based on the same sample still suggests the relatively slower growth rate of the SA comparing with the third group. Similarly, within the bilateral FPNs, neonatal structures are characterized by simple bilateral symmetric connectivity. Although smaller blobs in the left prefrontal cortex emerge at later ages, the resulting overall structures observed

in 1 year old are still far from those observed in adults. Therefore, it is likely that the SA and bilateral FPNs experience more significant maturation after the first year, suggesting that these 2 networks are the latest developing functional networks among the 9 networks examined. Since both networks, particularly the bilateral FPNs, are mainly associated with higher-order executive control and decision-making functions (Seeley et al. 2007; Vincent et al. 2008; Smith et al. 2009), this finding is consistent with the behavioral observations that higher-order cognitive functions require prolonged development over the life span (Rothbart 1990; Span et al. 2004; Zelazo et al. 2004; Dosenbach et al. 2010). However, caution should be undertaken in understanding the relationship between network topology and their functioning status since despite the latest topological maturation of SA and FPNs, certain preliminary forms of their functions such as salience detection, emotion assessment associated with the SA (Blasi et al. 2011; Alcauter et al. 2015; Arichi et al. 2013), and working memory function associated with the FPNs (Reznick et al. 2004) have been shown to be functioning during early infancy. Therefore, it is likely that the maturation of such higher-order cognitive networks represents an interactive process between the brain and behavior that evolves over long-life span (Johnson 2000). Interestingly, our results seem to suggest a faster development of the FPN L than the FPN R (Figs 3 and 4) during the first year of life despite the slow growth rates for both networks. This observation is largely in line with previous findings in similarly aged infants showing left-lateralized activation during presentation of either sentences (Dehaene-Lambertz et al. 2006) or phonemic auditory stimuli (Arimitsu et al. 2011), thought to support cognitive processes including short-term memory (Dehaene-Lambertz et al. 2006; Arimitsu et al. 2011). However, future studies are needed to more rigorously examine the asymmetrical development of functional networks during this critical period and their functional underpinnings and implications.

Effects of Socioeconomic Factors

Our results showed that higher income and higher maternal education were related to higher network matching scores and within-network connectivity in SM, while higher income was associated with lower outside-network connectivity in DMN. Both relationships indicate that higher SES (i.e., higher income or greater maternal education) corresponds with better network maturation (i.e., higher matching score with adult forms, higher within-network functional connectivity, or lower outside-network functional connectivity). SES has been documented to be related to different brain functions during development (Sarsour et al. 2011), but findings in this study revealed potential brain mediators of such relationship and point to the SM and DMN as particularly relevant in this role. More interestingly, all marginally significant SES–brain relationships were detected at a specific time point—6 months of age, suggesting the unique importance of this age in the expression of SES effects on functional connectivity. Interestingly, one recent study (Woods and Wilcox 2013) showed that babies' ability to sit up unsupported, which occurs right around 6 months of age, has a profound facilitating effect on their cognitive learning capabilities. Therefore, it is likely that functional connectivity at 6 months of age, featuring a dramatic change of body position in everyday activities that significantly impact cognitive learning (Woods and Wilcox 2013), may be particularly sensitive to the environmental opportunities that are largely dictated by SES. Therefore, babies with a more enriched environment (e.g., more toys to play with, more visits to cognitively stimulating places such as zoos or museums, and more parental attention on tasks such as reading and playing) may develop better sensory perception/motor coordination (associated with the SM) and quicker construction of self-consciousness (associated with the DMN). However, the fact that these correlations are only marginally significant (i.e., not surviving the multiple comparisons correction) and do not last during later time points suggests that a larger sample size is likely needed in future studies to validate the current findings. An important question for future studies is whether there are far-reaching effects that could be observed during school-age or adolescence following such early SES impacts on brain maturation. Nevertheless, the current results suggest that SES–brain correlations could be observed during the first year of life and are most salient around 6 months of age. These findings, if independently validated, could provide important information for future interventions or charity programs targeting improving the environment of babies from families with lower SES.

Several limitations deserve discussion. First, our delineation of the development of the pediatric functional networks was based on regions of interest (ROIs) defined from adult studies. We have previously used this strategy to define the brain's default and dorsal attention networks in similarly aged populations (Gao et al. 2012), and the results were highly consistent with those obtained using data-driven independent component analysis (Gao et al. 2009; Gao et al. 2014), providing support for the current approach. However, we do recognize that there is dramatic functional evolution between infants and adults, and a better way to define infant-specific functional ROIs is one of our future directions (Alcauter et al. 2015). Moreover, there could potentially be pediatric-specific functional networks that disappear in adults. Such networks could not be assessed using the currently adopted approach and deserve more data-driven approaches for further delineation. Secondly, there is a dramatic growth brain volume during the period studied and the effective voxel size (relative to the whole brain volume) is thus different across different time points (given the same absolute voxel size of 4 mm cubic). We recognized this factor and tried to normalize this difference by adaptively smoothing the data using age-specific Gaussian kernels as described in the Materials and Methods section. The results with and without this adaptive smoothing are highly consistent (Fig. 2 and Supplementary Fig. 1), indicating that our results are likely not driven by such relative voxel size differences. However, future studies are needed to more rigorously and more systematically study this effect.

Conclusions

With multiple longitudinal sampling during the critical first year of life, this study revealed the unique developmental patterns associated with 9 important functional networks. A developmental sequence starting from primary sensorimotor and auditory networks, to visual networks, to attention network and DMN, and finally to the salience and executive control networks was established. Moreover, network-specific critical periods of development were also revealed. These findings provide new insights into the early brain functional maturation process. The marginally significant correlations between functional

connectivity and socioeconomic factors observed at 6 months of age points to the potential importance of this time period for SES to impact early brain functional development.

Notes

Conflict of Interest: The authors declare no competing financial interests.

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