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Frequency of spontaneous BOLD signal shifts during infancy and correlates with cognitive performance

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ABSTRACT

Numerous studies have been conducted to delineate the early development of different functional networks, based on measuring the temporal synchronization of spontaneous blood oxygenation level-dependent (BOLD) signals acquired using resting state functional MRI (rsfMRI). However, little attention has been paid to the change of the frequency properties of these signals during early brain development. Such frequency properties may reflect important physiological changes and potentially have significant cognitive consequences. In this study, leveraging a large ($N = 86$ subjects), longitudinal sample of human infants scanned during the first two years of life, we aimed to specifically delineate the developmental changes of the frequency characteristics of spontaneous BOLD signals. Both whole-brain and network-level examinations were carried out and the frequency–behavior relationship was explored. Our results revealed a clear right-ward shift of BOLD signal frequency during the first year of life. Moreover, the power at the peak-frequency for sensorimotor and lateral visual networks correlates with domain-specific Mullen Scales in 1-year-olds, suggesting the behavioral significance of the BOLD signal frequency during infancy. Findings from this study shed light into early functional brain development and provide a new perspective for future searches for functional developmental abnormalities.

1. Introduction

The infancy period is arguably the most important period for human brain maturation, featuring both dramatic structural growth (Gilmore et al., 2007) and complex functional wiring (Tau and Peterson, 2010; Gao et al., 2014). To better delineate the functional brain development process during this critical period, numerous functional connectivity studies have been conducted (Fransson et al., 2007; Lin et al., 2008; Gao et al., 2009b; Smyser et al., 2010; Gao et al., 2014a; Gao et al., 2014). Functional connectivity measures temporal synchronization between the spontaneous blood oxygen level dependent signals (BOLD) (Biswal et al., 1995) and most studies using this technique focused on a fixed frequency band (e.g., between 0.01 and 0.08 Hz). However, the frequency distribution of BOLD signals likely changes with age (Allen et al., 2011), potentially reflecting underlying neurophysiological changes (Sambataro et al., 2010; Allen et al., 2011; Balsters et al., 2013; Fransson et al., 2013). Such age-dependent changes of the frequency

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characteristic of the spontaneous BOLD signals are likely the most dramatic during early brain development, since this period is characterized by the fastest development of closely related structural elements including axons, myelin sheath, synapses, dendrites, and astrocytes (Flechsig, 1901; Rakic et al., 1986; Rivera et al., 1999; Petanjek et al., 2008; Gao et al., 2009a; Petanjek et al., 2011; Gilmore et al., 2012a; Li et al., 2014). The development of these structural elements would likely impact neuronal signal transmission and neurovascular coupling, which may subsequently alter the frequency properties of the spontaneous BOLD signals. Importantly, the power of spontaneous BOLD signals at different frequency bands has been consistently linked to different cognitive performance measures including working memory (Sambataro et al., 2010; Balsters et al., 2013; Palacios et al., 2013). Moreover, its perturbation has also been implicated in different psychiatric disorders (Zang et al., 2007; Hoptman et al., 2010; Liang et al., 2014; Yu et al., 2014). Given the documented fast emergence of different cognitive functions during infancy (Johnson, 2000; Reznick, 2007; Tau and Peterson, 2010), it is thus imperative to study the changes of the frequency property of spontaneous BOLD signals during early brain development and explore its relationship with early cognitive performance.

Based on a large-scale longitudinal rsfMRI dataset covering the first two postnatal years, we aimed to explore the developmental changes in the frequency properties of the spontaneous BOLD signal. Specifically, the power spectral density (PSD) of the whole brain gray matter and its distribution within nine functional brain networks (Smith et al., 2009; Gao et al., 2014a; Gao et al., 2014) were explored. Given the well documented rapid synaptogenesis (Rakic et al., 1986; Elston et al., 2009), dendrite elaboration (Petanjek et al., 2008), astrocyte growth (Bandeira et al., 2009; Ge et al., 2012), and myelination (Flechsig, 1901) during the first year, which collectively could contribute to faster neuronal signaling and/or neurovascular coupling, we would expect a shift of the spontaneous BOLD PSD to higher frequencies during this period. In addition, given the observed correlation between BOLD frequency power and cognitive performance in adults (Sambataro et al., 2010; Balsters et al., 2013), we also hypothesized that the power of spontaneous BOLD signals will correlate with cognitive performance as assessed with the Mullen Scales of Early Learning (Mullen, 1995) at 1 and 2 years of age. Our results confirmed most of our hypotheses and provided new insights into early functional brain development.

2. Materials and methods

2.1. Subjects

Participants were part of a large study characterizing brain development in normal and high risk children (Gilmore et al., 2012b; Alcauter et al., 2014; Gao et al., 2014b; Gao et al., 2014). We retrospectively identified 118 healthy normal subjects (64 males) scanned at least twice during the first two years: neonates ($n = 111$, mean age = 33 ± 19 days), 1-year-olds ($n = 118$, mean age = 397 ± 36 days) and 2-year-olds ($n = 78$, mean age = 762 ± 35 days). The data included in this study have all been reported previously but with different analytic approaches (Gao et al., 2009b; Gao et al., 2011; Alcauter et al., 2013; Gao et al., 2013; Alcauter et al., 2014; Gao et al., 2014a; Gao et al., 2014b; Gao et al., 2014). Inclusion criteria were birth between gestational age of 35 and 42 weeks, appropriate weight for the 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 in the neonatal intensive care unit, mother with HIV, mother using illegal drugs/narcotics during pregnancy, and any chromosomal or major congenital abnormality. Informed written consent was obtained from the parents of all participants and all study protocols were approved by the University of North Carolina at Chapel Hill Institutional Review Board. Before imaging, subjects were fed, swaddled, and fitted with ear protection. All subjects were in natural sleep during the imaging session. A board-certified neuroradiologist (JKS) reviewed all images to verify that there were no apparent abnormalities.

2.2. Imaging

RsfMRI images of all finally included subjects were acquired with a 3 T Allegra head-only MR scanner (Siemens Medical systems, Erlangen, Germany), using a circular polarization head coil. Resting state fMRI (rsfMRI) was acquired using a T2*-weighted echo planar imaging sequence with repetition time (TR) = 2 s, echo time (TE) = 32 ms and voxel size of $4 \times 4 \times 4\,mm^3$. In total, 150 volumes of 33 axial slices were acquired in a 5 min scan. In order to provide anatomical reference, structural images were acquired using a 3D MP-RAGE sequence (TR = 1820 ms, TE = 4.38 ms, inversion time = 1100 ms), with a voxel size of $1 \times 1 \times 1\,mm^3$.

2.3. Data preprocessing

Functional data were preprocessed using FMRIB's Software Libraries (FSL, v 4.1.9) (Smith et al., 2004; Jenkinson et al., 2012). The preprocessing steps included discarding the first 10 volumes, slice-timing and motion correction. No spatial smoothing was applied. Mean signal from white matter, cerebrospinal fluid and six motion parameters were removed using linear regression. No global signal regression and no temporal filtering were performed for the main results. However, results with global signal regression were provided and compared. Further, the effect of low-frequency drift was assessed with a high-pass filtering of >0.01 Hz. In order to further reduce the effect of motion, the global measure of signal change and framewise displacement (FD) were controlled to be less than 0.3% signal and 0.2 mm, respectively, based on the most stringent version of the "scrubbing" process as previously proposed (Power et al., 2012, 2013). In order to avoid disruption of the time-series, only individual datasets with at least 90 contiguous volumes after scrubbing were further analyzed. The final sample included 112 brain scans of 86 subjects (36 males), distributed in three age-groups: neonates ($n = 36$, 13 males; mean age = 30.25 ± 17 days),

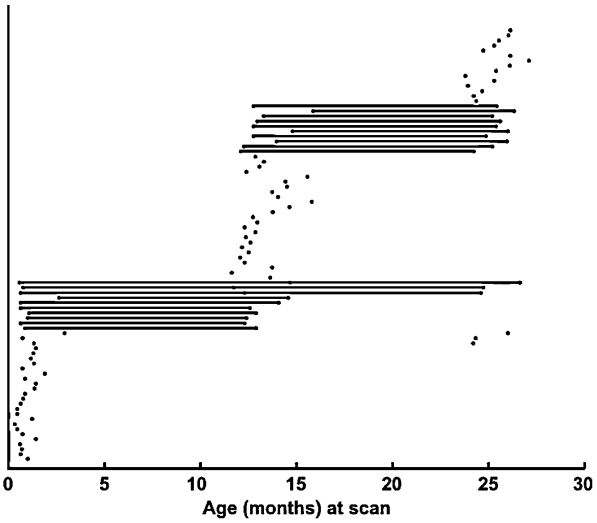

Fig. 1. The age distribution of the subjects included in this study.

1-year-olds ($n = 45$, 19 males; mean age = 397 ± 32 days) and 2-year-olds ($n = 31$, 15 males; mean age = 758 ± 25 days). The ages at which each subject was scanned are shown in Fig. 1. For each subject and session, after an initial rigid alignment between functional data and T1-weighted high resolution structural images, a nonlinear transformation field was obtained with FSL's fnirt (Smith et al., 2004; Jenkinson et al., 2012) from individual T1-weighted images to a longitudinal T1-template, i.e., T1-weighted images of a subject scanned at 2 weeks, 1 year and 2 years old. A combined transformation field was used to warp the preprocessed rsfMRI data to the longitudinal template. All quantitative power spectral density estimation (PSD) was performed in the longitudinal template space. Additionally, nonlinear transformation fields were obtained from the longitudinal template to the Montreal Neurological Institute (MNI) standard space using a 4-dimensional registration method, 4D-HAMMER (Shen and Davatzikos, 2004), which significantly improves warping accuracy over a series of independent 3D warping (Shen and Davatzikos, 2004). Comparisons of voxel-wise PSD values across age-groups were done on this common MNI space.

2.4. Power spectral density analysis

For each subject and session, only the first 90 continuous volumes were considered, to normalize the degree of freedom across subjects. For each voxel's time-series, power spectral density (PSD) was estimated using the periodogram method implemented in Matlab (R2011a, The Mathworks, Inc, Natick, MA, USA) and normalized by the total power. In order to estimate specific PSD for whole brain gray matter, the average PSD was calculated across all voxels within the brain regions defined by the AAL atlas (Tzourio-Mazoyer et al., 2002), previously warped to the longitudinal template. Analyses of covariance were performed for each frequency point to test for differences between groups in PSD, controlling for residual subject motion (measured as the average FD of the examined BOLD volumes). No sex difference in PSD was detected for any frequency point so it was not included in this comparison. Significant differences in the power at specific frequency values were detected at $p < 0.05$ level, after correcting for multiple comparisons using a false discovery rate (FDR) $q = 0.05$ (Benjamini and Yekutieli, 2001). For those frequencies with significant differences in PSD across groups, a Tukey-Kramer *post-hoc* test was carried out to identify the pairs of groups exhibiting significant differences. Subsequently, identical PSD analyses were carried out for nine functional networks previously studied (namely, the medial occipital network, the occipital pole network, the lateral visual/parietal network, the default-mode network, the sensorimotor network, the auditory/language network, the salience network, and the two lateralized frontoparietal networks) based on the same sample (Smith et al., 2009; Gao et al., 2014). Specifically, the masks for the nine networks defined in 2-year-olds were warped to the younger groups (Gao et al., 2014) and the average PSD was calculated for each network for subsequent across-group comparison.

In addition to whole brain level and network-level analyses, the voxel-wise spectral power at two specific frequencies, i.e., 0.0056 Hz and 0.0278 Hz, which correspond to the peak-frequencies for whole brain gray matter in neonates and 2-year-olds, respectively (Table 1), were also compared across groups. Two-group t-tests were performed to detect voxels showing significant PSD differences at each of the two peak frequencies across different age groups. Significance was defined at $p < 0.05$, after correcting for multiple comparisons (Benjamini and Yekutieli, 2001).

2.5. Cognitive performance correlation

Participants were assessed using the Mullen Scales of Early Learning (Mullen, 1995) at 1 year (mean = 12.29 ± 0.64, range = 11–15 months) and 2 years (mean = 24.33 ± 0.83, range = 22–28 months) of adjusted-age. The Mullen Scales evaluate five domains: visual reception, fine motor, gross motor, receptive language and expressive language. Normalized T-scores for each Scale within defined age groups range from 20 to 80, with a mean of 50 and a standard deviation of 10. In addition, the performance on the 4 cognitive Scales (excluding gross motor) are combined to create the conventional cognitive composite, or cognitive development index, the Mullen Early Learning Composite Standard Score (ELCSS), which ranges from 50 to 150, with a mean of 100 and a standard deviation of 15, similar to other overall tests of cognitive development, commonly referred to as IQ.

In order to explore the significance of PSD development on cognitive performance, the relationships between the power of the peak-frequency observed in 1- and 2-year-olds (i.e., 0.0278 Hz) and the Mullen Scale scores were explored using partial correlation, controlling for head motion (average FD of the 90 included volumes). Specifically, the partial correlation tests were performed between the PSD of whole brain and the global cognitive score, ELCSS, with statistical significance defined as $p < 0.05$. In addition, domain-specific correlations were explored

Table 1
Peak-frequency and frequency ranges with significant age-dependent changes in spectral power.

	Frequency with maximum spectral power (Hz)			Frequencies (Hz) with significant differences in spectral power between age-groups					
				Neonate – 1-year		Neonate – 2-year		1-year–2-year	
	Neonate	1-year	2-year	Neonate > 1-year	1-year > Neonate	Neonate > 2-year	2-year > Neonate	1-year > 2-year	2-year > 1-year
Gray matter	0.0056	0.0278	0.0278	0–0.0167, 0.2389	0.0278–0.0333, 0.1167	0–0.0111, 0.0556	0.0278, 0.1167–0.1389	0.05–0.0611,	–
Sensorimotor	0.0056	0.0278	0.0278	0–0.0111	0.0278–0.0333, 0.1167	0–0.0111, 0.0556	0.0278, 0.1278	0.0556	–
Auditory/ language	0.0056	0.0278	0.0278	0–0.0167	0.0278, 0.1278	0–0.0111	0.0278, 0.1278	–	–
Medial visual	0.0056	0.0333	0.0278	0–0.0167, 0.2389	0.0278, 0.0833, 0.1167–0.1278	0–0.0167	0.0278, 0.1167–0.1222	–	–
Occipital poles	0.0056	0.0333	0.0278	0–0.0111, 0.2222–0.25	0.0278–0.0333, 0.0889, 0.1167	0–0.0111, 0.2222–0.25	0.0278, 0.1167, 0.15	–	0.15
Lateral visual	0.0056	0.0278	0.0278	0–0.0111, 0.2–0.25	0.0278–0.0333	0–0.0111, 0.2222–0.25	0.0278–0.0333	–	–
Default mode	0.0056	0.0278	0.0278	0–0.0111	–	0–0.0111, 0.05	0.0278, 0.1167–0.1278	0.05	–
Salience	0.0056	0.0278	0.0278	0–0.0111	0.0278–0.0333, 0.1167–0.1389	0–0.0111	0.0278, 0.1167–0.1389	0.0333, 0.0611	-
Fronto-parietal left	0.0056	0.0278	0.0278	0–0.0111	0.0278–0.0333, 0.1167–0.1389	0–0.0111	0.0278, 0.1167–0.1444	–	–
Fronto-parietal right	0.0056	0.0278	0.0278	0–0.0167, 0.2389	0.0278–0.0389, 0.1167–0.1389	0–0.0167	0.0278, 0.1167–0.1389	0.0333–0.0611	–

between the PSD of visual ($n = 3$), sensorimotor ($n = 1$) and auditory/language ($n = 1$) networks with the corresponding cognitive scores, i.e., Visual Reception, Fine Motor, Receptive and Expressive Language scores, respectively, resulting in 6 domain-specific correlation tests (3 visual, 1 sensorimotor, and 2 language correlations). Significance was defined as corrected $p < 0.05$ based on FDR correction of the 6 correlation tests. To further validate our findings, for each correlation exhibiting a $p < 0.05$, a bootstrapping analysis was performed to identify the 95% confidence interval, based on 1000 times resampling with replacement.

3. Results

Comparison of the residual head motion parameter (i.e., average FD after scrubbing) showed smaller residual motion in neonates compared to older groups ($F(2,109) = 6.34$, $p = 0.003$; Tukey-Kramer HSD, $\alpha = 0.05$). No significant differences between 1- and 2-year-olds were observed (average residual FD ± standard deviation for neonate: 0.063 ± 0.013, 1-year: 0.071 ± 0.013, 2-year: 0.074 ± 0.011). Further comparisons of spectral power across age-groups were performed after controlling for residual head motion.

The power spectrum density of the whole brain gray matter (Fig. 2) showed significant and distinctive developmental patterns for the two typically defined frequency bands, i.e., the low frequency band ($f < 0.1$ Hz) and the high-frequency band ($f > 0.1$ Hz). Within the low-frequency band, neonates exhibited significantly greater power between 0 and 0.0167 Hz than both 1- and 2-year-olds. However, 1- and 2-year-olds showed increased power in the frequency range of 0.0278–0.0333 Hz, resulting in a clear right-ward shift in the peak-frequency with age: the PSD peaked at 0.0056 Hz for neonates and 0.0278 Hz for 1- and 2-year-olds (Fig. 2A, Table 1). Additionally, 2-year-olds showed decreased power in the frequency range 0.05–0.0611 Hz compared to both neonates and 1-year-olds (Fig. 2A, Table 1). In the high-frequency band (>0.1 Hz), the spectral power increased in both older groups compared with neonates within the frequency range of 0.1167–0.1389 Hz (Fig. 2A, Table 1). The changes in the PSD of the BOLD signal after global signal regression (Fig. 3A) and after high-pass filtering of the BOLD signal (Fig. 3B) were highly consistent with the original results, showing a clear rightward shift in the peak-frequency during development.

The voxel-wise spectral power at a frequency of 0.0056 Hz (i.e., the peak-frequency for neonates) and 0.0278 Hz (i.e., the peak-frequency for 2-year-olds) was visualized on brain surfaces for the three age groups in Fig. 2B and C. It is immediately clear that, at the whole brain level, neonates showed much higher power at the 0.0056 Hz frequency than both 1- and 2-year-olds while the two older age groups demonstrated much higher power at the 0.0278 Hz frequency than did neonates. Quantitative comparisons showed that the decrease of power in 0.0056 Hz during the first year is largely globally uniform (Fig. 2D) but the increase of the 0.0278 Hz power in the two older groups is less so (Fig. 2E). Particularly, the increase is largely focused in the posterior part of the brain, with the medial and lateral prefrontal regions largely void of significant increases (Fig. 2E). The changes in both frequencies during the second year of life were minimal.

The developmental patterns of the PSD for the nine functional networks were highly consistent with that of the whole brain (Fig. 4A and B; Table 1). Peaks of all the explored networks were consistently located in 0.0056 Hz for neonates and between 0.0278 and 0.0333 Hz for 1- and 2-year-olds (Fig. 4A). Quantitatively, neonates exhibited significantly greater power than both 1- and 2-year-olds between 0 and 0.0167 Hz (Table 1) while the two older groups showed greater power between 0.0278 and 0.0389 Hz (Fig. 4A, Table 1). For the gray matter, sensorimotor, default mode, salience and right frontoparietal networks, 2-year-olds exhibited additional decreases in the PSD for frequencies within the range of 0.0333–0.0611 Hz. In addition, the visual networks showed significant decreases between 0.2 and 0.25 Hz in the older groups. For most networks, older groups exhibited scattered increases between 0.1 and 0.15 Hz. Consistent with Fig. 2E, the age-related increases in PSD at the 1/2-year peak-frequency (i.e., 0.0278 Hz) was the strongest for the lateral visual, sensorimotor, auditory and default mode networks, followed by the medial visual and occipital poles networks while the frontal-lobe-centered bilateral frontoparietal and salience networks consistently showed the least increase for both 1- and 2-year-olds when compared with neonates (Fig. 4C).

Finally, the individual Mullen Scale scores showed positive correlations with the PSD in the peak-frequency (i.e., 0.0278 Hz; Fig. 5) in 1-year-olds. Specifically, the power of peak-frequency in the sensorimotor and lateral visual networks showed positive correlations with Fine Motor ($r = 0.365$, $p = 0.018$, bootstrapping confidence interval (c.i.): [0.058, 0.567]) and Visual Perception ($r = 0.339$, $p = 0.028$, c.i.: [0.085, 0.604]) scores, respectively. Although not significant after multiple comparisons correction, the confidence intervals established based on bootstrapping support their significance. The corresponding analyses in 2-year-olds showed no significant correlations.

4. Discussion

As numerous previous studies (Fransson et al., 2007; Gao et al., 2009b; Smyser et al., 2010; Fransson et al., 2011; Gao et al., 2011; Smyser et al., 2011; Alcauter et al., 2013; Gao et al., 2013; Alcauter et al., 2014; Gao et al., 2014a; Gao et al., 2014b; Gao et al., 2014) have delineated the synchronization process of different functional networks during infancy based on correlation measures of BOLD signals, one of the fundamental properties of BOLD signal, its frequency distribution, has been largely ignored. However, BOLD frequency has been consistently linked to both normal (Sambataro et al., 2010; Balsters et al., 2013; Palacios et al., 2013) and abnormal cognitive functioning (Zang et al., 2007; Hoptman et al., 2010; Liang et al., 2014; Yu et al., 2014) thus investigations into the frequency property of BOLD signals during infancy are highly deserved. Such an endeavor would likely provide us new insights beyond temporal synchronization of different functional networks and further the exploration of the brain basis for the

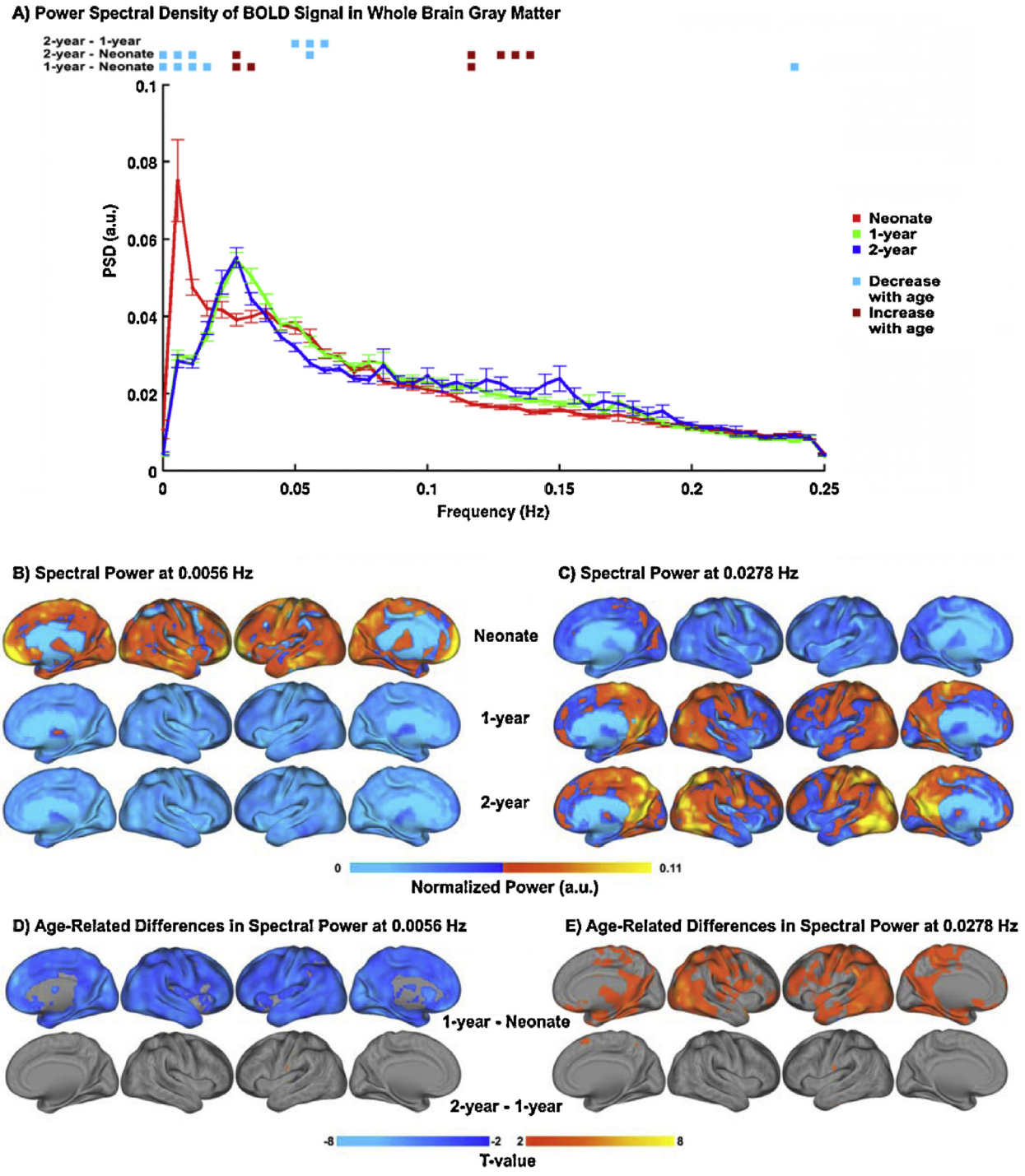

Fig. 2. Power spectral density (PSD) of spontaneous BOLD signal across the three age groups. (A) Average PSD of whole brain gray matter for neonates (red), 1-year-olds (green) and 2-year-olds (blue), error-bars denote standard error of the mean for each frequency point. Squares on top of the image denote significant decrement (light-blue) or increment (dark-red) with age for the corresponding frequency point ($p < 0.05$, FDR corrected, see Methods). (B) Spectral power at 0.0056 Hz for each age-group visualized on brain surfaces. (C) Spectral power at 0.0278 Hz for each age-group visualized on brain surfaces. (D) Significant differences on the spectral power at 0.0056 Hz across ages visualized on brain surfaces (cold colors: decrease; warm colors: increase). (E) Significant differences on the spectral power at 0.0278 Hz across ages visualized on brain surfaces (cold colors: decrease; warm colors: increase).

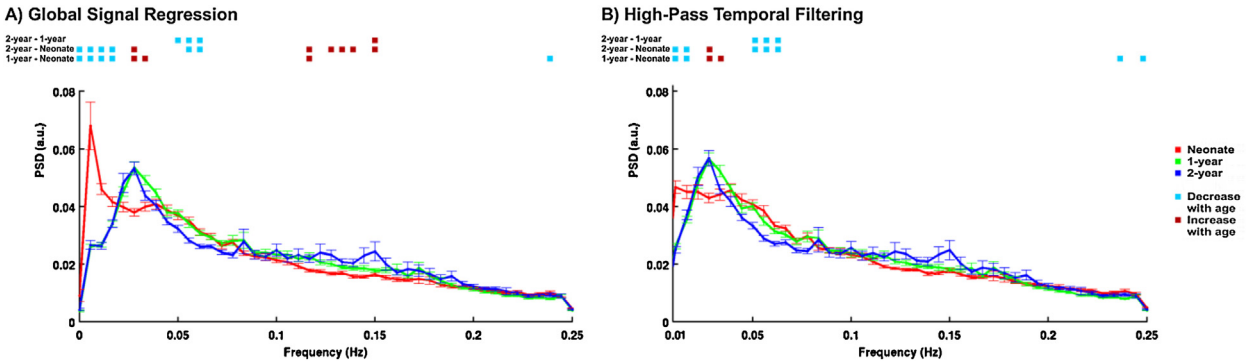

Fig. 3. Power spectral density (PSD) of spontaneous BOLD signal after global signal regression (A) and high-pass temporal filtering at 0.01 Hz (B). PSD of whole brain gray matter in neonates (red), 1-year-olds (green) and 2-year-ods (blue), error-bars denote standard error of the mean for each frequency point. Squares on top of the image denote significant decrement (light-blue) or increment (dark-red) with age for the corresponding frequency ($p < 0.05$, FDR corrected, see Methods).

emergence of different cognitive functions during this critical period of brain development. In this study, by systematically analyzing the PSD of the whole brain as well as nine specialized functional networks, our results revealed a clear rightward shift of the peak-frequency of spontaneous BOLD signal during the first year of life, resulting in an adult-like frequency profile. Moreover, the spectral power of the peak-frequency showed positive correlations with cognitive scores in 1-year-olds, stressing the relevance of such frequencies for cognitive development. To our knowledge, this is the first study directly delineating the early development of the frequency properties of the spontaneous BOLD signals and their cognitive correlations during infancy. The possible neurophysiological underpinnings and developmental implications are discussed below.

The rightward shift of the peak-frequency and the increased spectral power in the frequencies higher than 0.1 Hz evidence a general increase in the frequency of

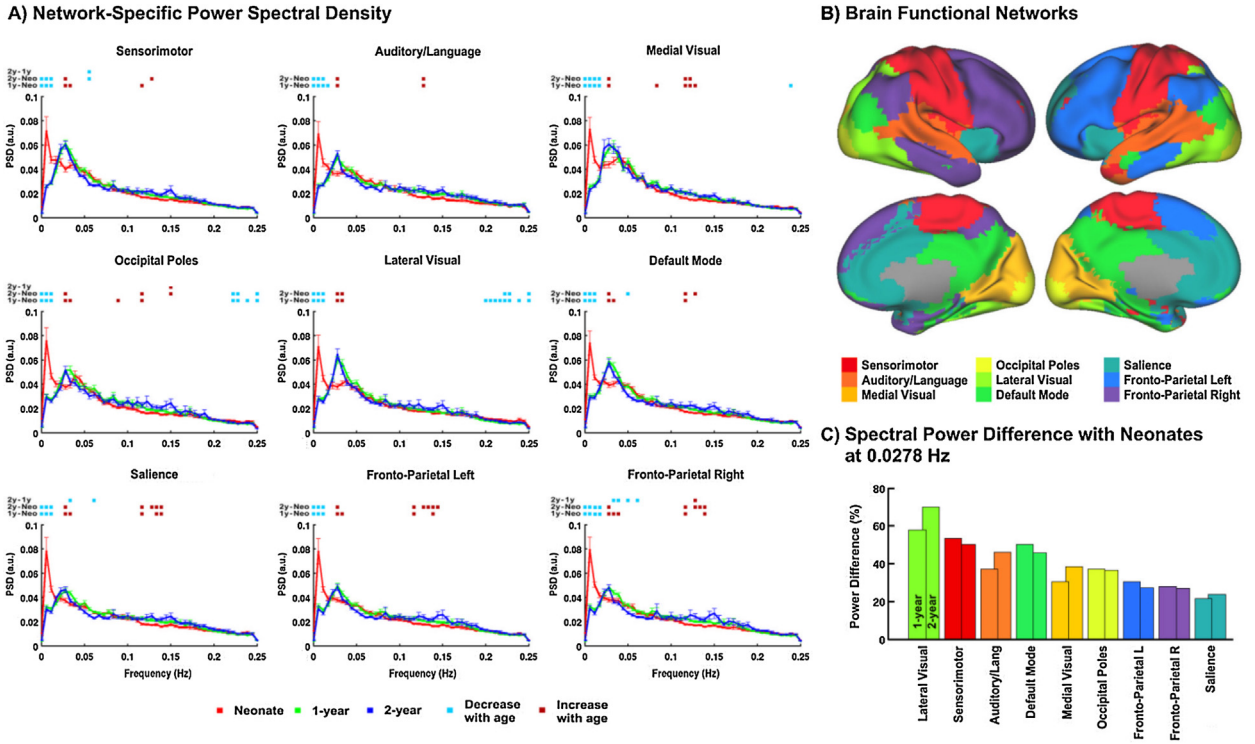

Fig. 4. Power spectral density (PSD) of spontaneous BOLD signal in 9 functional brain networks across the three age groups. (A) Network-specific PSD curves for neonates (red), 1-year-olds (green) and 2-year-olds (blue), error-bars denote standard error of the mean for each frequency point. Squares on top of each graph denote significant decrement (light-blue) or increment (dark-red) with age for the corresponding frequency ($p < 0.05$, FDR corrected, see Methods). (B) The masks of the nine functional brain networks explored are visualized on brain surface. (C) Spectral Power difference between 1-year-olds (first of each pair of bars) and 2-year-olds (second of each pair of bars) and neonates at the peak-frequency of 2-year-olds (i.e., 0.0278 Hz) for each network.

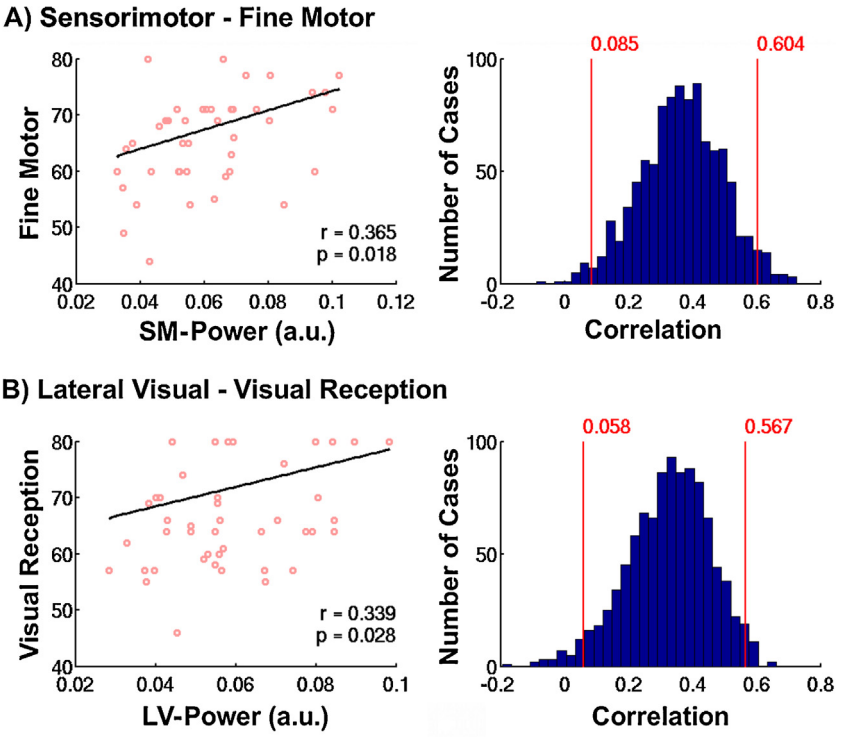

Fig. 5. Spectral power of the peak-frequency correlates with cognitive performance in 1-year-olds. (A) Significant positive correlation between the spectral power for the sensorimotor (SM) network and the Mullen Fine Motor Scale score. (B) Significant positive correlation between the spectral power for the lateral visual (LV) network and the Mullen Visual Perception Scale score. Circles represent individual subjects, the black line represents the linear fit, after controlling for residual head movement (frame-wise displacement). Histograms represent the distribution of the partial correlation values for 1000 bootstrapped samples, red values and lines represent the 95% confidence interval.

spontaneous BOLD fluctuations during the first year of life. This increment in frequency likely results from more efficient signal transmission, which is in line with the observed fast myelination (Flechsig, 1901), dendritic elaboration (Petanjek et al., 2008; Freeman, 2010), synaptogenesis (Rakic et al., 1986; Huttenlocher and Dabholkar, 1997; Elston et al., 2009), and astrocyte proliferation (Bandeira et al., 2009; Ge et al., 2012), which all show their most significant development during the first year after birth. These structural events likely collectively promote faster neuronal signaling and/or neurovascular coupling, thus enhancing the frequency of the observed BOLD signal. Such an increase in frequency is also consistent with the observed significant increase in glucose metabolism during the first year (Chugani et al., 1987). The non-linear developmental trend of the frequency property of the spontaneous BOLD signal is in line with numerous previous studies showing the most dramatic development in different functional networks (Gao et al., 2013; Alcauter et al., 2014; Gao et al., 2014a; Gao et al., 2014) and in system efficiency properties (Gao et al., 2011) during the first year.

The peak-frequency reported in adults is between 0.015 and 0.02 Hz (Biswal et al., 1995; He et al., 2014) while the peak-frequency is 0.0278 Hz for 1- and 2-year-olds, suggesting a possible overshooting of peak-frequency during infancy. Early overshooting and subsequent refinement may represent a universal phenomenon for different developmental events (Tau and Peterson, 2010). The frequency overshooting observed in this study may be underpinned by the initial overproduction of the neurophysiological facilitators of signal-transmission and neurovascular coupling such as synaptogenesis, axons, and astrocytes (Rakic et al., 1986; Chugani et al., 1987; Elston et al., 2009; Petanjek et al., 2011). In contrast, the subsequent pruning of different elements during later development (Rakic et al., 1986; Huttenlocher and Dabholkar, 1997; Elston et al., 2009; Tau and Peterson, 2010; Petanjek et al., 2011) may contribute to the gradual decrement of peak-frequency to its observed adult level. Consistently, Allen et al. (2011) observed a decreasing trend of the low-frequency power from 12 years of age to adulthood. Collectively, findings in this study support that an adult-like frequency profile of spontaneous BOLD fluctuations is established by 1 year of age but with a potential overshooting in the peak-frequency.

The spectral power at the neonatal peak (i.e., 0.0056 Hz) showed largely uniform decreases during the first year (Fig. 2D). However, the developmental trend at the peak-frequency of 2-year-olds (i.e., 0.0278 Hz) showed spatially dependent patterns (Fig. 2E). Specifically, more increases were observed in the posterior portions of the brain, including the pre- and post-central gyri, lateral occipital and temporo-occipital cortices, medial posterior parietal lobe and auditory cortices (Fig. 2C and E) during the first year of life. This finding seems to be in line with the outstanding development of motor control (Corbetta

and Thelen, 1996; Forssberg, 1999), visual acuity, spatial attention (Haith et al., 1988; Courage and Adams, 1990) and auditory discrimination (Chang and Trehub, 1977; Trehub et al., 1987) around this age. The rapid increase of the spectral power for the medial posterior regions of the default-mode network may be related to the emergence of self-awareness (Amsterdam, 1972; Uddin et al., 2007). In contrast, the medial and lateral prefrontal cortices showed the least increase. Consistently, at the network level, the frontal-lobe-centered salience and frontoparietal networks showed the least increase in the peak-frequency spectral power (Fig. 4C). This trend is highly consistent with our recently delineated developmental sequence of different functional networks (Gao et al., 2014a) and is in line with the hierarchical model of brain development, suggesting that the prefrontal lobe shows the latest development (Stuss, 1992; Gogtay et al., 2004; Elston et al., 2009). In fact, prefrontal-related executive functions are documented to continue to develop until adolescence and young adulthood (Welsh and Pennington, 1988; Luna et al., 2010). Therefore, findings in this study re-emphasize this general developmental trend but from a novel frequency perspective.

The positive correlations between the power in the peak-frequency and domain-specific cognitive scores observed in 1-year-olds (Fig. 5) strongly support the relevance of frequency development to cognitive performance. Specifically, the power at the peak-frequency for sensorimotor and lateral visual networks showed positive correlations with the corresponding fine motor and visual perception scores (Fig. 5). These findings are consistent with the behavioral milestones achieved at this age, including motor control (Corbetta and Thelen, 1996; Forssberg, 1999), visual acuity, and spatial attention (Haith et al., 1988; Courage and Adams, 1990). These findings are also consistent with a recent report that BOLD signal frequency indexes cognitive performance in adults (Balsters et al., 2013). However, our results suggest that such frequency–behavior relationships emerge very early during development (i.e., by 1 year of age). The fact that no significant frequency–behavior correlations were observed in 2-year-olds is intriguing. It is possible that the development of primary functions dominates the first year of life while by the end of the second year, such processes may have already reached plateau (with the exception of language) and the variability-based frequency–behavior relationships may have shifted towards other higher-order functions that may not be tapped by the broad Scale scores on the Mullen. Future studies are needed to investigate this possibility.

In addition to the changes observed in the low-frequency band, the most consistent change with age was the increased spectral power in the frequency range between 0.1167 Hz and 0.15 Hz. Although this frequency band was not typically included in most functional connectivity studies, there are studies showing the functional relevance of frequencies up to 0.2 Hz (Feinberg et al., 2010; Niazy et al., 2011). There are also reports suggesting that increased spectral power for frequencies higher than 0.1 Hz are related to decreased functional connectivity in schizophrenia (Garrity et al., 2007), bipolar disorder (Calhoun et al., 2011) and chronic pain (Malinen et al., 2010; Baliki et al., 2011). Thus, the developmental changes for the high-frequency band may also be functionally meaningful and deserve further investigation.

4.1. Influence of non-neural sources and limitations

Spontaneous fluctuations of BOLD signal at frequencies higher than 0.1 Hz are frequently contaminated by motion artifacts (Cordes et al., 2001; Kim et al., 2013). However, the results presented here are unlikely driven by motion-related artifacts: First, a set of stringent motion correction criteria (Power et al., 2012, 2013) allowed for the selection of minimally motion-affected data. Secondly, our comparisons of spectral power across groups were performed after controlling for residual head motion, providing more direct evidence that the observed developmental changes are not secondary to motion artifacts. On a side note, although our main analyses were based on the 90 continuous volumes after scrubbing to minimize motion artifacts, our analyses of the whole time series (after despiking (Gotts et al. (2013)) and regression of the motion parameters, Fig. S1) revealed highly consistent patterns, further supporting the robustness of our results against different motion correction strategies. However, the lack of external monitoring of cardiac and respiratory effects indeed represents one potential limitation of the present study. Nevertheless, the changes in the PSD of the BOLD signal after global signal regression were highly consistent with the original results (Fig. 3A), which seems to suggest the robustness of our results against potential physiological confounders (Chang and Glover, 2009). Moreover, we have repeated our analyses in gray matter as well as in a set of manually defined white matter and CSF regions after omitting the regression step of the corresponding white matter and CSF signals in the preprocessing steps (Fig. S2). While the observed frequency shift in gray matter still holds after omitting the regression step, it is not observed for white matter or CSF regions, further supporting the neuronal relevance of the observed frequency property change. However, we do notice the persistence of the very low-frequency peak in neonates across the three types of regions which might reflect potential partial volume effect (which is expectedly most severe in neonates given the smallest brain sizes and worst image contrast). Nevertheless, we could not fully rule out the contribution of non-neuronal factors to the observed low-frequency peak in neonates based on our data alone. Future studies are needed to more rigorously dissect the underpinnings of this very low frequency peak. Regarding a potential concern about low-frequency drift, the analyses of the high-pass filtered BOLD signal (>0.01 Hz, Fig. 3B) again showed a clear rightward shift in the peak-frequency during development, suggesting that our main conclusion is not driven by low-frequency drift artifacts either.

5. Conclusions

In conclusion, findings in this study revealed a rightward shift of the frequency distribution of spontaneous BOLD signals during the first year resulting in an adult-like profile by 1year of age. In addition, the power of the

peak-frequency in 1-year-olds correlates with cognitive performance, suggesting strong behavioral significance for the development of BOLD signal frequencies. These findings add novel knowledge to our understanding of early brain functional development and suggest that frequency properties are important features for future delineation of both normal and abnormal brain maturation.

Conflict of interest

All authors declare no competing financial interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dcn.2014.10.004.

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