



Exploring functional brain activity in neonates: A resting-state fMRI study

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ABSTRACT

The human brain is born with a certain maturity, but quantitatively measuring the maturation and development of functional brain activity in neonates remains a topic of vigorous scientific research, especially the dynamic characteristics. To address this, T1w, T2w, and resting-state functional magnetic resonance imaging (rs-fMRI) data from 40 full-term healthy neonates and 38 adults were adopted in this study. Group differences of local brain activity and functional connectivity between neonates and adults from both static and dynamic perspectives were explored. We found that the neonatal brain is largely immature in general. Sensorimotor areas were the most active, well-connected, and temporally dynamic. Compared with adults, visual and primary auditory areas in neonates showed higher or similar local activity but lower static and dynamic connections with other brain regions. Our findings provide new references and valuable insights for time-varying and local brain functional activity in neonates.

1. Introduction

The neonatal brain is the result of complex and genetically programmed developmental trajectories with adult-like cortical gyrification and large-scale white matter tracts in place at birth (Ball et al., 2014; Keunen et al., 2017). Based on the earlier maturation of brain structures, the functional brain undergoes tremendous development at this early stage (Gilmore et al., 2018). The thalamocortical connectivity forms as early as midfetal period (Thomason et al., 2015) and is crucial for the whole brain maturation and later cognitive outcomes (Alcauter et al., 2014; Antón-Bolaños et al., 2019; Ball et al., 2015; Poh et al., 2015; Toulmin et al., 2015). Qualitative adult-like sensorimotor, auditory, and visual networks have been consistently reported as primary functional networks in neonates (Cao et al., 2017b; Fransson et al., 2009; Gilmore et al., 2018; Smyser et al., 2010). Meanwhile, compared with adult networks, high-order functional networks seem quite immature (Gao et al., 2017; Zhang et al., 2019), such as networks involved in language, social interaction, memory, and executive control functions.

Besides the popular functional networks analysis, it is of great significance to probe into the local brain activity since the segregated functions exist in early brain development (Fair et al., 2009; Hagmann et al., 2010; Huang et al., 2015). A recent study (Long et al., 2017) examined age-related functional brain changes of 44 children aged 2–6

years employing amplitude of low frequency fluctuation (ALFF) (Zang et al., 2007), fractional amplitude of low frequency fluctuation (fALFF) (Zou et al., 2008), and regional homogeneity (ReHo) (Zang et al., 2004). ALFF and ReHo in the frontoparietal regions are positively correlated with age, while ALFF in the sensorimotor, auditory, and visual areas reduce linearly with age. ALFF and ReHo have been used to explore abnormal brain activity in deaf infants and preterm neonates (Wu et al., 2016; Xia et al., 2017). Nevertheless, local brain activity in healthy term neonates remains poorly understood.

Beyond the static perspective of functional brain activity, temporal dynamic features of the brain have attracted more and more attention (Chang and Glover, 2010; Hindriks et al., 2016; Preti et al., 2017). During infancy, functional connectivity (FC) dynamics of the whole-brain and high-order functional networks increase with age while FC dynamics within sensorimotor and visual networks decrease (Wen et al., 2020). Exploring dynamic neural interactions in early life can further our understanding of functional flexibility and the establishment of the functional brain organization, and still, not much work has been done in neonates.

Local brain activity and temporal dynamics of the healthy term neonates are little studied but of great implications for understanding normal brain development. Comparing functional brain activity or connectivity of neonates with those of adults helps us describe the

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maturation of functional brain at birth quantitatively, which is a valuable and meaningful topic in early brain development (Gao et al., 2009; Pendl et al., 2017; van den Heuvel et al., 2014). In this study, we compared local brain activity and functional connectivity of neonates with those of adults from both static and dynamic perspectives in a variety of indices, including ALFF, fALFF, ReHo, dynamic ALFF, dynamic fALFF and dynamic ReHo (Tang et al., 2018), FC, standard deviation of FC (sdFC), and regional dynamic FC (rdFC) (Zhang et al., 2016). We hypothesized that compared with adults, group differences of local brain activity and functional connections would be observed in large-scale brain regions in neonates, and static and dynamic indices of primary function areas may be found higher at birth since they were reported decreased in later years in previous studies (Long et al., 2017; Wen et al., 2020).

2. Materials and methods

2.1. Participants

T1- and T2- weighted images and rs-fMRI data of 40 healthy neonates (25 males) were acquired from a current large-scale project: *Developing Human Connectome Project* (dHCP) (Hughes et al., 2017), Release 1. All participants were born at full term (gestational age >37 weeks) and were scanned in a range of gestational age from 37 to 44 weeks (see <http://www.developingconnectome.org> for more details). The data from four neonates were excluded due to the registration failure, thus there was a total of 36 neonate participants in the final study. T1w images and fMRI data of 38 healthy adults were obtained from a publicly available dataset: S900 Data Release from *Human Connectome Project* (HCP) (Van Essen et al., 2013), and the average age of adult participants was 28.7 (± 3.65) (see <https://www.humanconnectome.org> for more details).

2.2. Data acquisition

All neonates were scanned during natural sleep on a Philips Achieva 3 T scanner equipped with a dedicated neonatal imaging system and a neonatal 32 channel phased array head coil at the Evelina Neonatal Imaging Centre, St Thomas' Hospital, London. Multiband (MB) 9x accelerated echo-planar sequence with 2.15 mm isotropic resolution (repeated time (TR) = 392 ms, time echo (TE) = 38 ms) was performed for infant brain during 15 min. To reduce the impact of the subtle head motion during sleep, we extracted continuous 800 volumes (around 5 min) according to the quality control files provided by dHCP groups and tried to ensure most of the chosen volumes would not have big head motion. MRI acquisition for adults was carried out on a Siemens Skyra 3 T scanner located at Washington University in St. Louis, State of Missouri. Gradient echo EPI sequence with 2 mm isotropic resolution (TR = 720 ms, TE = 33.1 ms, FOV = 208 × 180 mm², matrix = 104 × 90 with 72 slices) was performed during around 15 min for four runs. To get in line with the extracted volumes of neonates, continuous 400 volumes (about 5 min) were chosen for each adult.

2.3. Data preprocessing

Functional images of neonates and adults were preprocessed by dHCP (Fitzgibbon et al., 2019) and HCP teams (Glasser et al., 2013) respectively. Briefly, the functional preprocessing steps for neonates included correction of susceptibility distortions, motion correction, registration to T2w structural images, high-pass filter (150 s), and ICA denoising. Functional preprocess pipeline for adults consisted of gradient distortion correction, motion correction, distortion correction, EPI to T1w images registration, intensity normalization to a global mean, and bias field removal.

Considering distinct appearances of neonatal and adult brain and the great difficulty of spatial normalization, we conducted the whole study

in each participant's native functional volume space. To avoid possible errors in nonlinear registration between atlases and the data we used and to reduce noise in images, we analyzed the data at the regional level using age-specific AAL atlases (Shi et al., 2011; Tzourio-Mazoyer et al., 2002) (details in Supplementary Table S1) with 90 regions of interest (ROI). For each participant, firstly, age-specific AAL atlas was registered to the T2w image (for infants) or T1w image (for adults) using FMRIB's Linear Image Registration Tool (FLIRT) (Jenkinson et al., 2002; Jenkinson and Smith, 2001) for linear registration and Statistical Parametric Mapping (SPM) (Friston et al., 1994) for nonlinear registration (trilinear interpolation method in the two software), as suggested in (Shi et al., 2011). Secondly, tissue-labeled mask and AAL atlas in native structural space were transformed into individual functional space using FLIRT (neonates data with the transformation matrix between T2w and functional images from the dHCP team).

2.4. Static and dynamic local brain activity

Researchers have implemented several approaches to explore local brain activity, such as ALFF, fractional ALFF (fALFF), and ReHo, which were involved herein. ALFF was introduced to measure the intensity of regional spontaneous neural activity (Zang et al., 2007) within a low frequency range, while fALFF approach is interpreted as the ratio of low-frequency spectral power (e.g. 0.01–0.08 Hz) to that of the entire frequency range (Zou et al., 2008), which was proved to improve the sensitivity and specificity in detecting spontaneous brain activity. The ReHo approach is based on the Kendall coefficient of concordance, representing the synchronization of time series between one given voxel and its nearest 26 neighbors (Zang et al., 2004). The number of neighbors 26 was chosen for more robustness to noise when compared to 6 or other numbers of neighbors.

In this study, we employed the methods from our previous work (Tang et al., 2018) and explored temporal variability of local brain activity during the scan, i.e., d-ALFF, d-fALFF and d-ReHo. The dynamic measures are combinations of sliding-window technique and three static measures (ALFF, fALFF, and ReHo), and the calculation can be characterized as three steps (Fig. 1 as an example using HCP datasets): for each subject, firstly, segment the time series of every voxel into overlapping fixed-length time windows (window length $l = 40$ s, step size $s = 1$ TR), resulting in 698 time windows for dHCP datasets and 345 time windows for HCP datasets; secondly, compute the value of ALFF, fALFF and ReHo in each time window; thirdly, calculate the coefficient of variation (CV) across a series of time windows, which was obtained by dividing the standard deviation by the mean as d-ALFF, d-fALFF, and d-ReHo. See Tang et al. (2018) for a more detailed explanation of the calculation process. Spatial smoothing was applied with different Gaussian kernels (Full width at Half Maximum of 4 and 6 mm for neonates and adults, respectively) after the individual feature maps were obtained. The choice of Gaussian kernels is determined according to different brain sizes of the two groups. Specifically, the neonatal brain volume is about 35 % of adults' (Gilmore et al., 2007), and then the ratio of kernel radius for neonates and adults is defined as the cubic root of 35 %, which is closed to 4:6.

2.5. Functional connectivity (FC) and dynamic functional connectivity (dFC)

The traditional functional connectivity (FC) analysis was included in this study to probe the functional wiring pattern in the two age groups, which calculated the pairwise Pearson correlation coefficient across the whole brain. The human brain activity exhibits time-varying fluctuations, therefore, dynamic functional connectivity (dFC) was also introduced in this paper to investigate temporal variability of neural activity. Combined with sliding window correlation technique, two different measures of dFC were applied (Fig. 1): the first measure was standard deviation of FC (sdFC) which evaluated the standard deviation of the

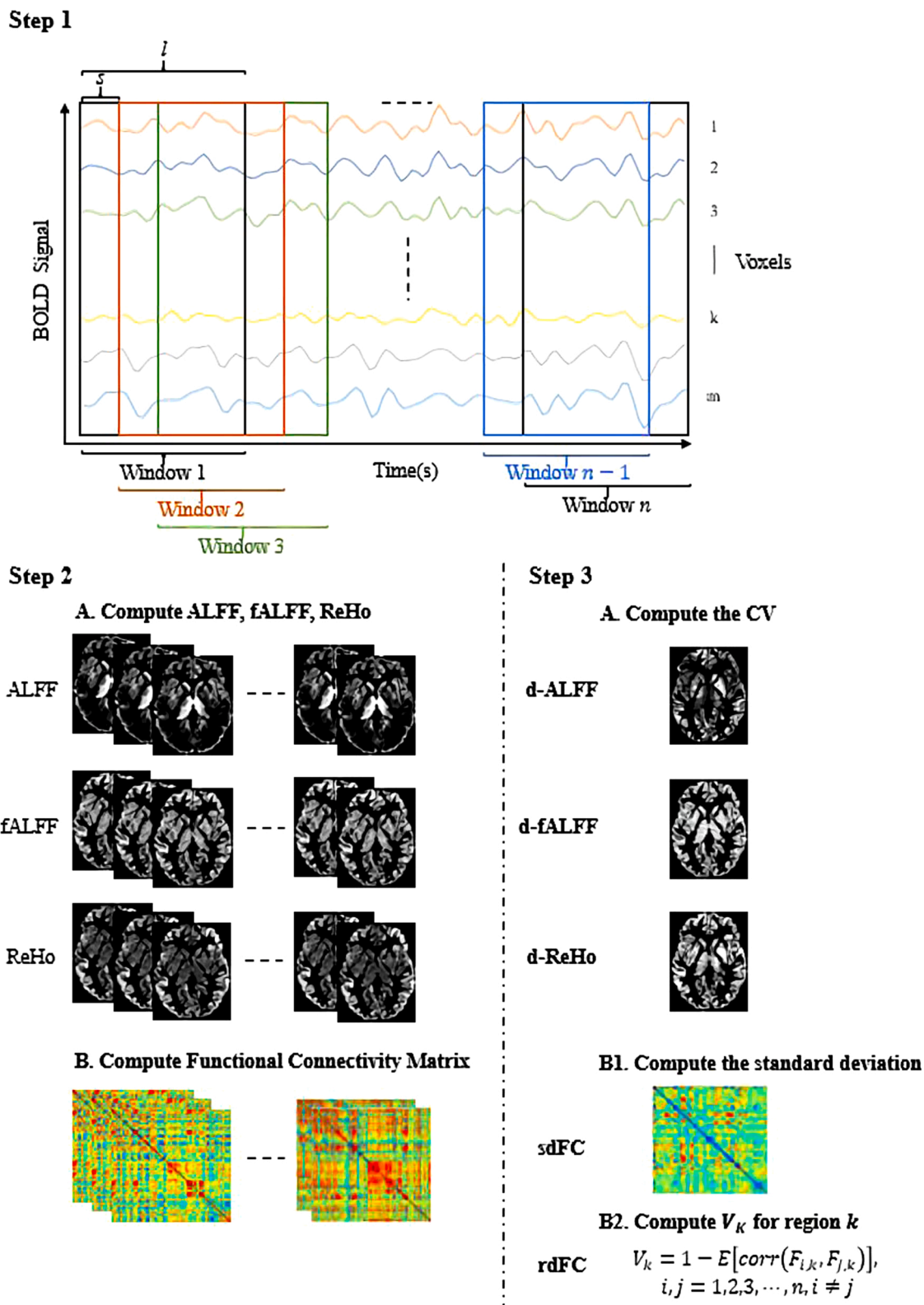


Fig. 1. An example calculation process of dynamic measures using HCP datasets. **Step1**: segment the time series of each voxel into a series of overlapping windows with length l and step size s ; **Step 2A**: compute the value of ALFF, fALFF, and ReHo in each time window; **Step 2B**: obtain correlation matrix of 90 ROI in each time window; **Step 3A**: compute the coefficient of variation (CV) across time windows as d-ALFF, d-fALFF and d-ReHo; **Step 3B1**: to get sdFC, calculate the standard deviation of the correlation coefficient of each pair of ROI across time windows; **Step 3B2**: to get rdFC of region k (V_k), compare functional connectivity profiles of region k at different time windows using the Formula (1).

correlation between each pair of ROI across time windows, and the second measure was regional dynamic FC (**rdFC**) (J. Zhang et al., 2016) which explored temporal variability of the functional architecture associated with a given region. The parameters of time windows were the same as that in Section 2.4.

The first step of the calculation of dFC was the same as that of dynamic local brain activity, which could obtain a series of time windows. The second was to acquire the FC matrix of 90 ROI in each time window. For **sdFC**, the third was to calculate the standard deviation of the correlation coefficient of each pair of ROI across time windows. For **rdFC** of region k , V_k is defined as:

$$V_k = 1 - E[\text{corr}(F_{i,k}, F_{j,k})], \quad i, j = 1, 2, 3, \dots, n, \quad i \neq j \quad (1)$$

where i and j denote the window number, n is the total number of time windows, $F_{i,k}$ and $F_{j,k}$ denote connectivity profile of region k to all other regions at time window i and time window j , respectively.

2.6. Statistics analysis

To avoid possible errors in voxelwise registration which may largely influence the accuracy of group comparison, the whole analysis was conducted at ROI-level. Considering the overall group differences of absolute values of local brain activity in these two populations, mean normalized values (subtracting the group mean and dividing by the group standard deviation) were used. The average value of each ROI in all local brain activity was obtained for each subject. Each participant, therefore, had six vectors with 90 values in each vector for local brain measures, one 90*90 matrix for FC, one 90*90 matrix for **sdFC**, and one vector with 90 values for **rdFC**. Besides, to better understand functional maturation in the neonatal brain, the averaged absolute values across the brain in the two groups were compared using a two-sample t -test for each local activity measure ($P < 0.05$).

To explore group differences of static and dynamic local activity and functional connectivity between neonates and adults, two-sample t -tests were performed. Significance correction for multiple comparisons (90 times for local activity measures and **rdFC**, and $90*89/2 = 4005$ times for connectivity measures) was applied using the Bonferroni approach at a significant level of $P < 0.05$. The whole statistical analysis was performed in MATLAB R2017b.

2.7. Validation and reproducibility study

To validate the main findings in the dynamic measures, we considered one additional time window length (50 s) with one TR as a step unchanged in each group and repeated the dynamic analysis described in Sections 2.4 and 2.5. To evaluate the reproducibility of our results, another randomly picked and gender-matched 38 adults data from HCP were used and were compared to dHCP data in functional brain measures mentioned in Sections 2.4 and 2.5.

3. Results

3.1. Local activity measures

Compare with adults, the overall absolute values of ALFF ($P < 0.0001$), fALFF ($P < 0.0001$), ReHo ($P = 0.0271$), and d-ALFF ($P < 0.0001$) of neonates were significantly smaller, while d-fALFF of neonates was larger ($P < 0.0001$). There were no significant group differences in the global mean of absolute values of d-ReHo ($P = 0.4211$).

To compare regional group differences of static and dynamic local brain activity between neonates and adults, ALFF, fALFF, ReHo, d-ALFF, d-fALFF, and d-ReHo maps were calculated for each subject. Mean normalized values (subtracting the group mean and dividing by the group standard deviation) were used on individual smoothed maps, and then the averaged value of each ROI was extracted. If not indicated

otherwise, the results presented in the results and discussion parts were for mean normalized data.

The mean maps of the three static and three dynamic measures within each group were provided in Figs. 2 and 3, respectively. Overall, the neonatal brain showed different local functional activity/synchronization patterns from the adult brain, featuring relatively higher values of fALFF/ReHo/d-ReHo in the precentral gyrus (preCG), postcentral gyrus (poCG), medial parietal and occipital cortex when compared with the rest of the brain.

As shown in Figs. 4 and 5 (details in Supplementary Table S2–3), neonates showed larger ALFF predominantly in basal ganglia (putamen and pallidum, maximum corrected $P < 0.0001$), precuneus (corrected $P < 0.0001$), visual cortex (fusiform gyrus (FFG), cuneus, lingual gyrus (LING), and inferior occipital gyrus (IOG), maximum corrected $P = 0.0001$), auditory cortex (Heschl gyrus (HES) and superior temporal gyrus (STG), maximum corrected $P = 0.0009$), and limbic/paralimbic regions (median and posterior cingulate cortex, hippocampus, parahippocampus gyrus (PHG), and amygdala, maximum corrected $P = 0.0342$) and larger d-ALFF in sensorimotor cortex (preCG, poCG, paracentral lobule (PCL), maximum corrected $P = 0.0009$), superior and inferior temporal gyrus (maximum corrected $P = 0.0068$), lateral prefrontal cortex (maximum corrected $P = 0.0098$), lateral parietal cortex (maximum corrected $P = 0.0106$), medial superior frontal gyrus (SFG, maximum corrected $P = 0.0269$). Adults showed larger ALFF mainly in the lateral and medial prefrontal cortex (maximum corrected $P < 0.0001$), inferior temporal gyrus (ITG, maximum corrected $P < 0.0001$), orbital cortex (maximum corrected $P < 0.0001$), thalamus (maximum corrected $P = 0.0164$), limbic regions (anterior cingulate and paracingulate gyri (ACG) and hippocampus, maximum corrected $P = 0.0397$) and larger d-ALFF in subcortical areas (pallidum, putamen, caudate, and thalamus, maximum corrected $P < 0.0001$), FFG (corrected $P < 0.0001$), precuneus (corrected $P = 0.0018$), IOG (maximum corrected $P = 0.0219$), limbic/paralimbic regions (middle and posterior cingulate cortex, olfactory, orbital cortex, amygdala, hippocampus, PHG, insula, maximum corrected $P = 0.0414$).

In comparison with adults (Figs. 4 and 5, Supplementary Table S2–3), neonates showed larger static and dynamic fALFF and ReHo predominantly in sensorimotor cortex (preCG, poCG, PCL, and supplementary motor area (SMA), maximum corrected $P = 0.0103$), superior parietal gyrus (SPG, maximum corrected $P = 0.0142$), precuneus (maximum corrected $P = 0.0387$), and cuneus (maximum corrected $P = 0.0481$), while adults showed larger static and dynamic fALFF and ReHo mainly in hippocampus (maximum corrected $P = 0.0021$), subcortical areas (maximum corrected $P = 0.0060$), and lateral and medial inferior temporal lobes (maximum corrected $P = 0.0377$). Although group differences seemed to be similar among these measures, the spatial distribution pattern of local activity of each measure was distinct from one another as revealed by group mean maps in Figs. 2 and 3.

3.2. Functional connectivity measures

The average FC analysis results (Fig. 6) revealed an adult-like functional connectivity pattern in neonates, but still in an immature form. Further statistical analysis (Fig. 7A, Supplementary Table S4) found that when compared with adults, a large number of brain regions in neonates appeared to show lower functional connectivity with other regions than that of adults.

As shown in Fig. 7B (Supplementary Table S5), with regards to **sdFC**, neonates appeared to show higher **sdFC** between STG and preCG/poCG (maximum corrected $P = 0.0226$), and among LING, cuneus, calcarine fissure and surrounding cortex (CAL), and superior occipital gyrus (SOG) (maximum corrected $P = 0.0427$), which involved in sensorimotor, auditory, and visual regions. A great number of brain regions were observed lower temporal variation in neonates than that in adults converging in frontal regions (maximum corrected $P = 0.0484$), basal

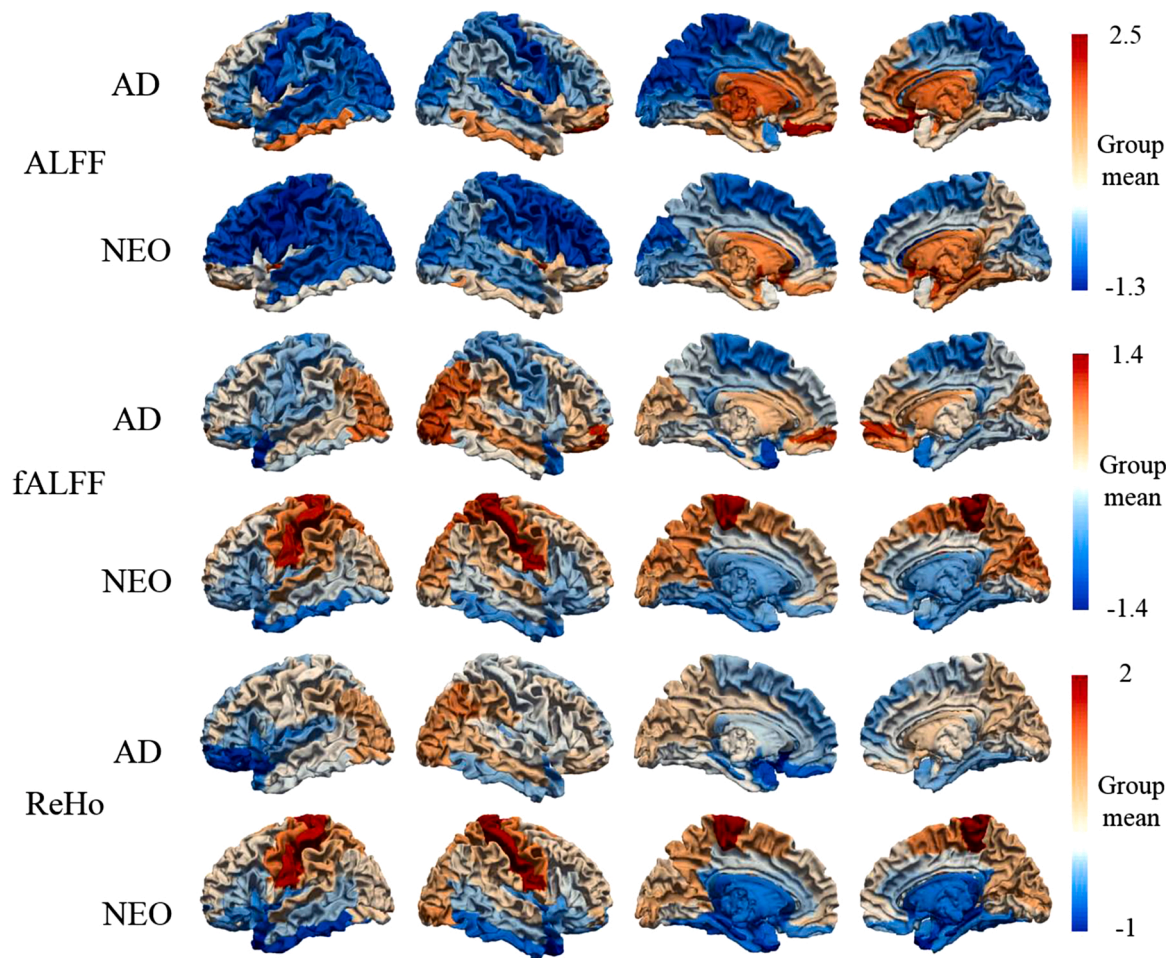


Fig. 2. The normalized group mean maps of static local brain activity of adults and neonates.

ganglia (maximum corrected $P = 0.0499$), and limbic/paralimbic regions (maximum corrected $P = 0.04998$).

As shown in Fig. 7C (Supplementary Table S6), neonates showed higher **rdFC** in bilateral LING (maximum corrected $P = 0.0182$), but lower **rdFC** in bilateral basal ganglia (maximum corrected $P = 0.0239$) and limbic/paralimbic areas (amygdala, olfactory, and orbital cortex, maximum corrected $P = 0.0388$).

3.3. Validation and reproducibility results

To test the reliability of our dynamic results, we used the 50 s as time window length and repeated the dynamic analysis. The validation analysis largely replicated the main findings in Sections 3.2 and 3.3 (Supplementary Figs. S1–S2). Group differences of dynamic ALFF in the lateral prefrontal cortex and subcortical regions were not found between neonates and adults. To evaluate the reproducibility of our study, we randomly picked another HCP datasets and repeated the same analysis processes. The results suggested high reproducibility of group differences of functional brain activity between neonates and adults (Supplementary Figs. S3–S4).

4. Discussion

In this study, to comprehensively investigate the functional brain development at birth, we compared the neonatal brain with the adult brain from static and dynamic perspectives using local activity and functional connectivity measures at ROI level. We found that in comparison to adults, neonates showed 1) higher static and dynamic local

activity in sensorimotor areas; 2) higher or comparable levels of static local activity in visual and primary auditory areas; 3) lower static and dynamic local activity in subcortical areas; 4) different patterns of local activity in limbic/paralimbic regions and association cortex; 5) much lower dynamic connections across the brain except the sensorimotor cortex. See Table 1 as a summary.

4.1. Development of primary function regions in the neonatal cerebral cortex

Sensorimotor areas are the most active and well-connected regions in the neonatal brain. This can be supported by the adult-like functional activity in these regions (Allievi et al., 2016; Dall'Orso et al., 2018) and by the early maturation of sensorimotor network in a series of neonatal fMRI studies (Cao et al., 2017a; Gao et al., 2015b; Lin et al., 2008). Sensorimotor functions assist the interaction with the external world and the adaptation to the changing environment, which is essential for basic survival and later prolonged cognitive development. We also demonstrated that neonates exhibit comparable temporal dynamics with adults in functional connectivity measures in sensorimotor areas, which suggests relatively mature functional flexibility of these active areas at birth. Neonates were observed higher or similar local brain functional activity with that of adults in static situations in visual and primary auditory areas. The findings are largely in line with the reported adult-like capability of infants or fetuses in sensory processing (Lagercrantz and Changeux, 2010) and responses to visual and auditory stimuli (Fulford et al., 2003; Wild et al., 2017). However, the overall connectivity and connectivity flexibility in these regions were still lower than

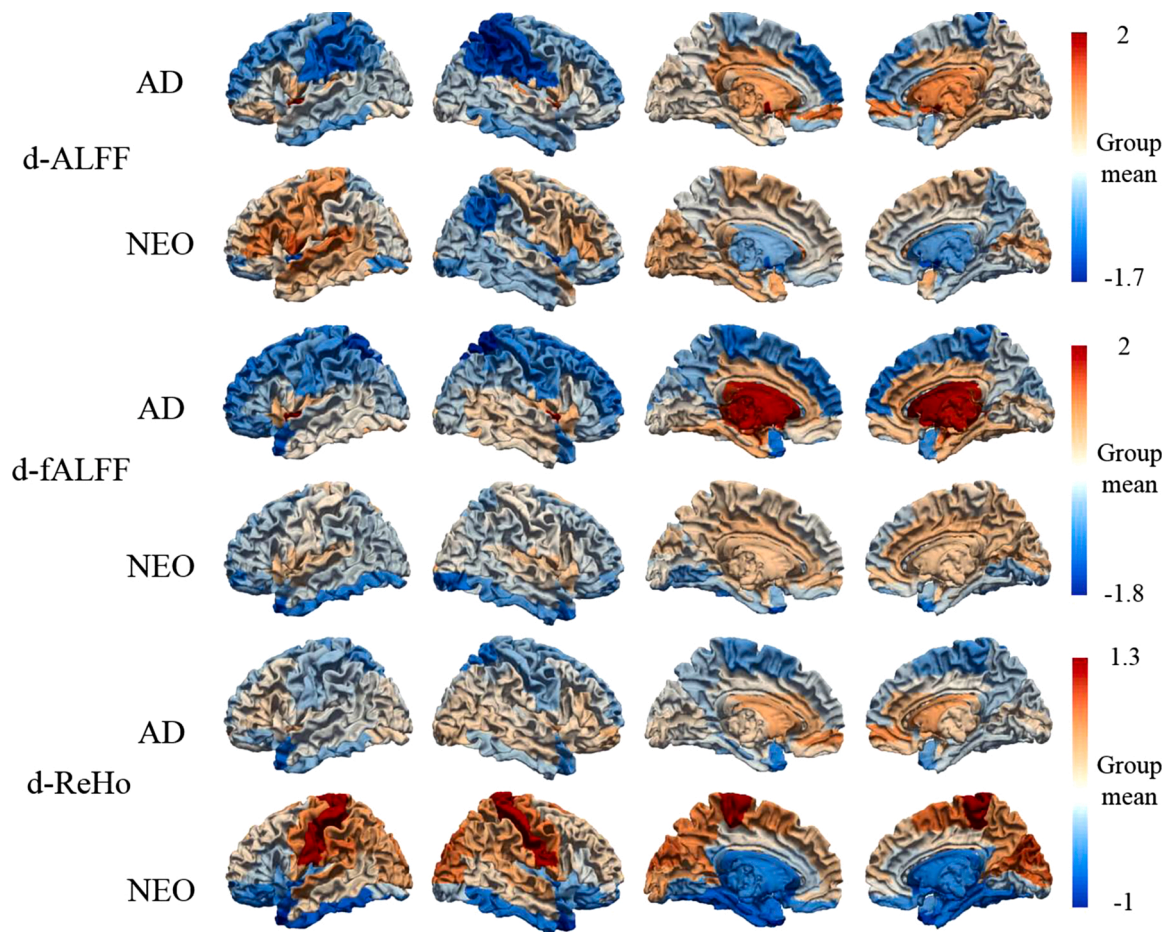


Fig. 3. The normalized group mean maps of dynamic local brain activity of adults and neonates.

that of the mature brain, perhaps due to the incomplete synaptogenesis and myelination at this very early time point (Tau and Peterson, 2010).

In the present study, we found some metrics of primary function areas in the neonatal brain higher than the counterparts in the mature brain (static and dynamic local activity of sensorimotor cortex, static local activity of auditory cortex, and sdFC within occipital cortex), which might indicate a descending trend of these metrics after birth. Previous studies have reported decreased static local activity in sensorimotor and auditory areas in 2–6 years old children (Long et al., 2017) and decreased FC temporal dynamics within the visual network in 0–2 years old infants (Wen et al., 2020), which indirectly reveal higher static and dynamic metrics in primary function areas at the start of postnatal life. It is worth noting that what we focus on is the functional brain maturity at a specific time point, and the comparison results cannot be used to estimate the developing trends since there is a large age gap between neonates and adults.

4.2. Development of subcortical, limbic/paralimbic areas and association cortex in the neonatal brain

Group differences of functional activity and connectivity between the two populations were observed in a great number of brain regions, especially in subcortical, limbic/paralimbic regions, and high-order association cortex, which reflected the quite immature functional organization in these regions. Group mean maps of FC (Fig. 6) showed lower connectivity in subcortical and limbic/paralimbic regions than other brain regions in both two groups, which is consistent with prior studies in adults' or neonatal FC (Cao et al., 2017a; Farras-Permanyer et al., 2019), and the connectivity strength in these regions in neonates was

found lower than that in adults by visual inspection. Neonates showed much lower local activity in subcortical areas, suggesting relatively weaker activity strength and functional synchrony. The lower static and dynamic connectivity here may indicate weaker subcortico-subcortical and subcortico-cortical connections in the immature brain, but the connections will increase with age (Cao et al., 2017a; Wen et al., 2020). To note, there were very few group differences of static FC in the thalamus, indicating relatively closer connections between the thalamus and the rest of the brain when compared with other subcortical structures. The thalamus serves a critical role in the relay center of sensory and motor signals and pacemaker of the whole brain (Jones, 2000) and is supposed to correspond to the active sensorimotor function in newborns, as revealed by the findings of strong thalamocortical connectivity in the sensorimotor network (Smyser et al., 2016). Lower local brain functional activity in the limbic system may partially due to the lack of emotion, motivation, memory, and learning behaviors in neonates who do not have enough social or emotional experiences yet. Lower FC temporal variability in these limbic/paralimbic regions possibly indicates a more stable functional state in the neonatal brain. A recent infant study in dynamic FC has reported interesting findings that limbic/striatum network remains unchanged in temporal connections to other networks with age increases (Wen et al., 2020), which also implies a stable state and independent activity of these regions at early age.

The development of association cortex in the neonatal brain is more complicated. Plenty of association regions particularly frontal lobes were found group differences using static and dynamic ALFF, which indicates much less and temporally unstable local activity in low frequency (0.01–0.08 Hz) in the undeveloped brain, whereas much fewer group differences were found using static and dynamic fALFF and ReHo,

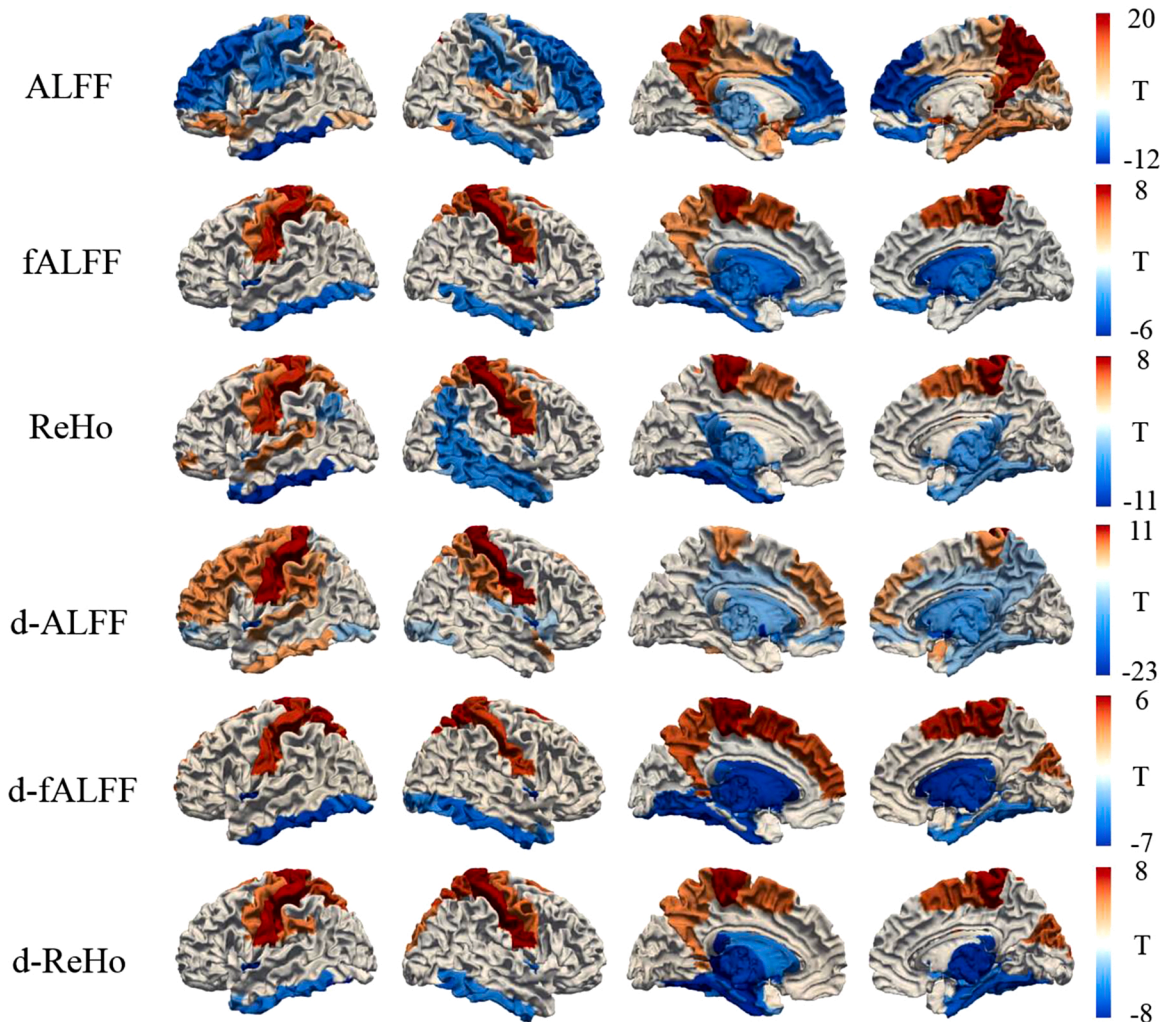


Fig. 4. The group differences of static and dynamic local brain activity between neonates and adults. The first three rows were for static local brain activity, and the last three rows were for dynamic local brain activity. The red color indicates that the measure of neonates is statistically greater than that of adults, while the blue color indicates the opposite. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

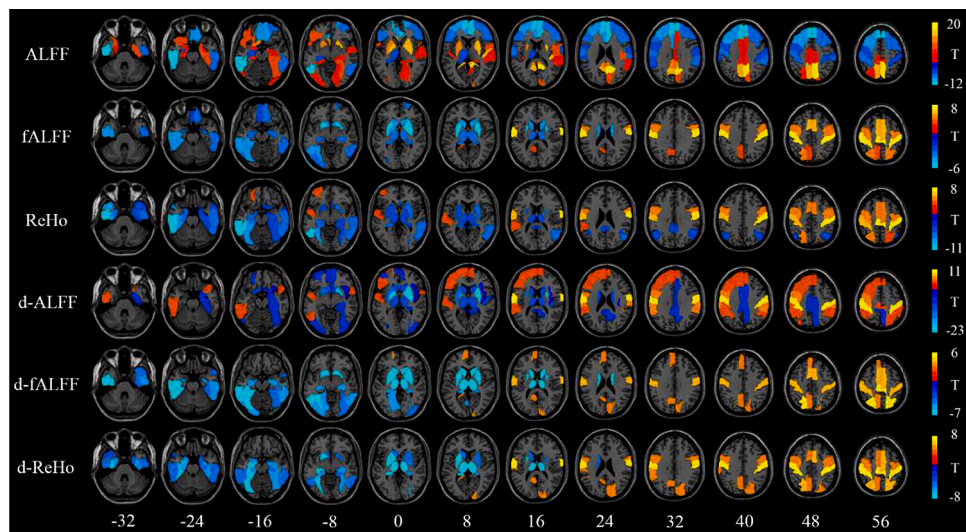


Fig. 5. Volumetric T maps of group differences of static and dynamic local brain activity between neonates and adults. The warm/yellow-red color indicates that the measure of neonates is statistically greater than that of adults, while the cool/blue-light blue color indicates the opposite. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

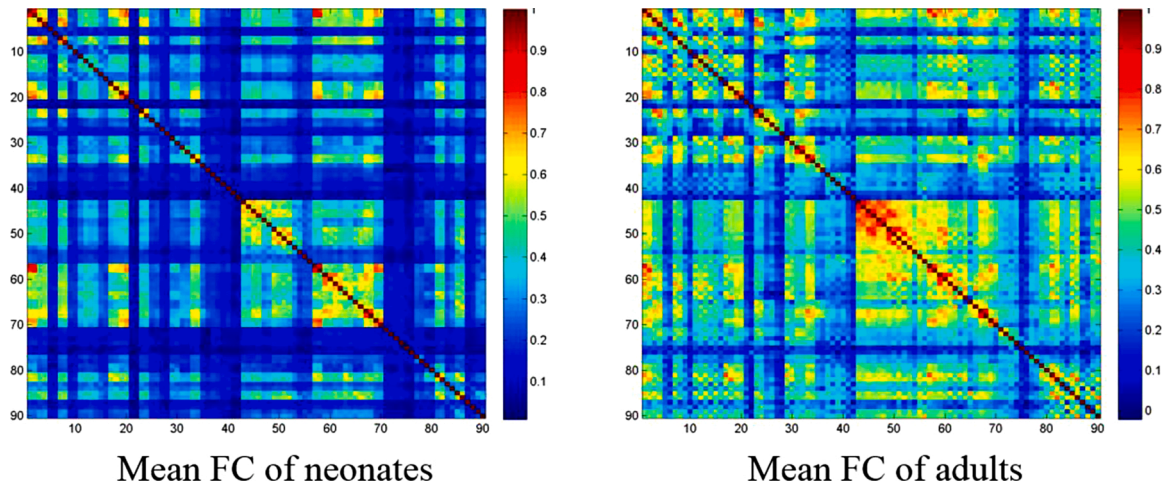


Fig. 6. The average FC matrix of neonates and adults.

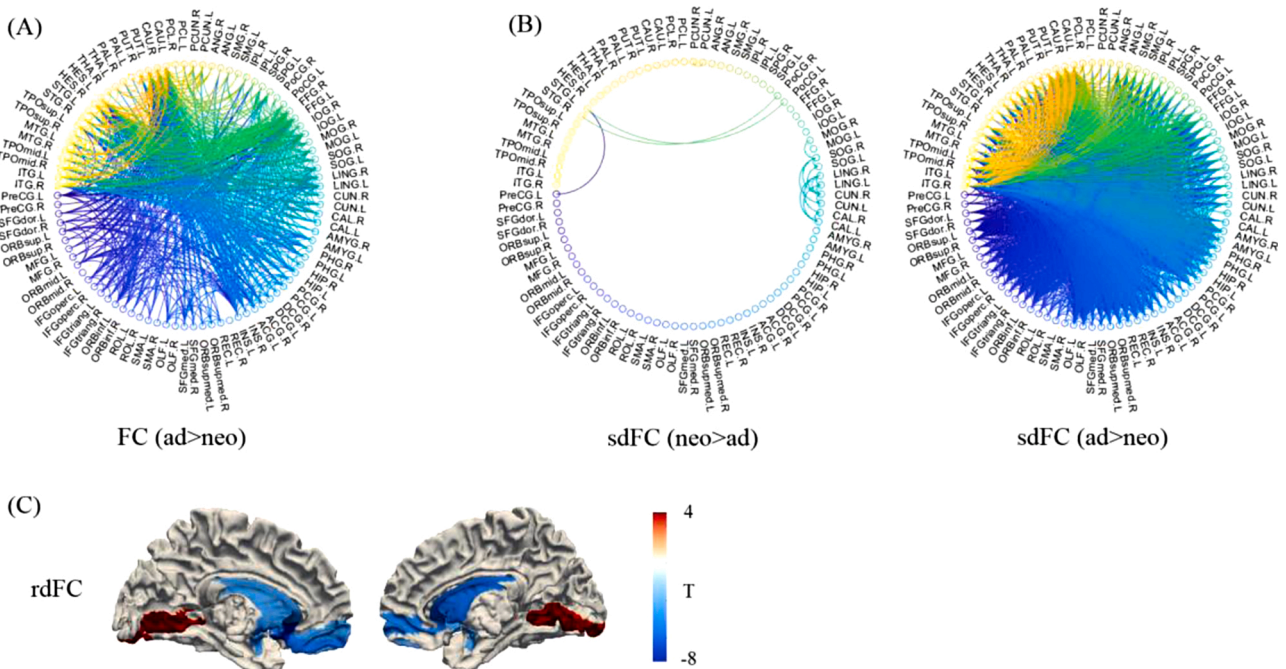


Fig. 7. The group differences of FC, **sdFC**, and **rdFC** between neonates and adults. neo: neonates; ad: adults. (A) The group differences of FC between neonates and adults. (B) The group differences of **sdFC** between neonates and adults. (C) The group differences of **rdFC** between neonates and adults. The red color indicates that **rdFC** in the region of neonates is statistically greater than that of adults, while the blue color indicates the opposite. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

which suggests more maturity in regional relative activity than total activity and also more maturity in local connectivity. Together with lower FC of association regions, the results suggest that the development of short cortico-cortical connectivity prior to the distant ones, as summarized in (H. Zhang et al., 2019). In the same vein, lower dFC indicates that association regions of the neonatal brain are not flexibly connected with other regions as those of adults, but FC dynamics will grow in the following years (Wen et al., 2020). It is important to note that group differences of absolute global means were observed in five of six local activity measures, indicating overall immaturity in terms of local activity in neonates. Among all the measures, adults showed increased activity or connectivity in temporal association cortex especially the FFG and ITG, which suggests undeveloped functions in inferior temporal lobes in early life.

It is not surprising to find the neonatal brain largely immature. The

brain and cognitive abilities mature in interactions between the environment and individuals (Johnson, 2001), especially the maturation of high-order brain regions, which can last for years (Diamond, 2002). Several regions in association cortex are important nodes of high-order functional networks, such as default mode, attention, and frontoparietal networks. In particular, frontoparietal networks associated with executive control or decision-making will continue to develop in later age (Gao et al., 2015a; Wen et al., 2019), and related regions will show more activity and synchronization in early childhood (Long et al., 2017). As the brain matures, the global FC temporal variability will gradually increase, as well as the FC dynamics within and between high-order functional networks (Wen et al., 2020).

Table 1
Group differences in functional brain activity between neonates and adults.

Measures	Static local activity	Dynamic local activity	Static FC	Dynamic FC
Sensorimotor areas	NEO>AD	NEO>AD	AD \geq NEO	AD \geq NEO
Visual and primary auditory areas	NEO \geq AD	AD \geq NEO	AD>NEO	AD>NEO
Subcortical areas	AD>NEO	AD>NEO	AD>NEO	AD>NEO
Limbic/paralimbic areas	AD \geq NEO	AD \geq NEO	AD \geq NEO	AD>NEO
Temporal association cortex	AD \geq NEO	AD \geq NEO	AD>NEO	AD>NEO
parietal association cortex	NEO \geq AD	NEO \geq AD	AD \geq NEO	AD>NEO
Frontal association cortex	AD \geq NEO	NEO \geq AD	AD \geq NEO	AD>NEO

NEO: neonates, AD: adults; **Sensorimotor areas:** preCG, poCG, PCL, and SMA; **Visual and primary auditory areas:** SOG, MOG, IOG, cuneus, LING, CAL, and HES; **Subcortical areas:** thalamus, pallidum, caudate, and putamen; **Limbic/paralimbic areas:** amygdala, hippocampus, cingulate cortex, olfactory, PHG, orbital cortex, insula, and temporal pole; **Temporal association cortex:** STG, MTG, ITG, FFG; **parietal association cortex:** SPG, IPL, SMG, ANG, and pre-cuneus; **Frontal association cortex:** SFG, MFG, IFG, and ROL.

4.3. Multi-views to investigate the development of the neonatal brain

Since brain networks of neonates are found highly immature in previous studies (Cao et al., 2017b; Zhang et al., 2019), only local activity and connectivity are studied in this paper. Regional fluctuation properties (ALFF and fALFF) and inter-regional correlation properties (FC) of the neonatal brain are thoroughly investigated to further our understanding of early brain development. ReHo measures temporal synchrony between each voxel and its neighbors, which refers to local connectivity to some extent. Static indices measure properties of brain activity or connectivity for the whole time, while dynamic indices measure the temporal changes of these properties across different time windows. The intrinsic relationship among these measures of brain functional activity still remains unclear to date. A previous study reported a high degree of concordance between fALFF and ReHo and also between d-fALFF and d-ReHo with subjects aged 45 on average (Yan et al., 2017). Notably, they found subcortical and limbic areas less concordance among different measures and high CV for fALFF across time windows, which is consistent with some of our findings (Figs. 2 and 3).

Temporal variation of the resting brain has been highlighted in numerous studies on adults and children (Chai et al., 2017; Hutchison et al., 2013; Marusak et al., 2017; Preti et al., 2017). Dynamic indices reveal essential time-varying features of the brain that enable possibilities of switching diverse cognitive functions at different times and interactions with rapidly changing environments. Nevertheless, there is very limited exploration of temporal variability in newborn babies. A recent study explored age-related changes in FC temporal variability from 0 to 2 years (Wen et al., 2020). In the present study, we used not only connectivity but also local activity to evaluate temporal dynamics of the neonatal brain. The values of d-ALFF were higher in lateral and medial prefrontal regions in neonates than those in adults, which may indicate weak stability of these future cortical hubs. In adults, d-ALFF/fALFF of prefrontal regions were relatively low, but d-ReHo of these regions were high since they highly connected with other brain regions and support complex functions, as shown in Fig. 3, which was supported by a previous study (Yan et al., 2017). High values of d-ReHo mean that voxels switch functional synchronization with their neighbors or distant voxels frequently, which may imply complicated temporospatial information processes in this region, as proved by a prior dynamic FC study (Zhang et al., 2016). Higher global mean values of d-fALFF in neonates may suggest instability of regional brain activity in one specific frequency in this population. Two measures of dFC were

employed here. Apparently, **sdFC** is more sensitive to group differences of temporal changes in connectivity since it measures each pair of ROIs, while **rdFC** measures the regional profile. Both two dynamic measures detected inter-group differences in temporal variability of functional connectivity in the basal ganglia, limbic/paralimbic, and visual regions.

4.4. Technique concerns and limitations

Temporal dynamics have been widely explored in the adult, child and infant's brain (Marusak et al., 2017; Wen et al., 2020; Zhang et al., 2016), and there seem no technical concerns over applications of these dynamic methods to the neonatal brain. The choices of time window length followed suggestions by (Leonardi and Van De Ville, 2015), who proposed 30–60 s as reasonable window lengths. Our validation analysis using the 50 s as window length yielded largely similar results.

A limitation that should be considered is that neonates and adults were scanned in two consciousness states, but to what extent the results are attributed by different consciousness states remains unknown. Usually, neonates sleep 14–17 h a day (Hirshkowitz et al., 2015) and sleeping is the most normal state for them. It is hard to include awake newborns during MRI scan, so imaging during natural sleep is one of the most commonly used approaches in neonates and infants studies (Zhang et al., 2019). Additionally, dHCP and HCP datasets were collected using different scanner types, which may produce undesirable effects on results. Apart from the scanner type, other factors such as different scanner parameters and head coils used in the neonatal and adult fMRI can also result in negative effects. Future studies may endeavor to resolve these practical and technical issues in the comparison of functional brain activity between neonates and adults.

5. Conclusion

In this paper, we quantified the differences of local brain activity and functional connectivity between neonates and adults using a number of measures from both static and dynamic perspectives. In general, the neonatal brain is largely immature in quantitative functional activity and connectivity. Compared with other brain regions, sensorimotor areas were the most active and well-connected, as well as temporally dynamic. Compared with the adult brain, visual and primary auditory areas in the neonatal brain showed higher or similar local activity but lower static and dynamic connections. Our study provides valuable insights into functional brain activity and connectivity in neonates from multiple aspects.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.dcn.2020.100850>.

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