fNIRS-Based Dynamic Functional Connectivity Reveals the Innate Musical Sensing Brain Networks in Preterm Infants

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***Abstract*—Humans have the ability to appreciate and create music. However, why and how humans have this distinctive ability to perceive music remains unclear. Additionally, the investigation of the innate perceiving skill in humans is compounded by the fact that we have been actively and passively exposed to auditory stimuli or have systematically learnt music after birth. Therefore, to explore the innate musical perceiving ability, infants with preterm birth may be the most suitable population. In this study, the auditory brain networks were explored using dynamic functional connectivity-based reliable component analysis (RCA) in preterm infants during music listening. The brain activation was captured by portable functional near-infrared spectroscopy (fNIRS) to simulate a natural environment for preterm infants. The components with the maximum inter-subject correlation were extracted. The generated spatial filters identified the shared spatial structural features of functional brain connectivity across subjects during listening to the common music, exhibiting a functional synchronization between the right temporal region and the frontal and motor cortex, and synchronization between the bilateral temporal regions. The specific pattern is responsible for the functions involving music comprehension, emotion generation, language processing, memory, and sensory. The fluctuation of the extracted components and the phase variation demonstrates the interactions between the extracted brain networks to encode musical information. These results are critically important for our understanding of the underlying mechanisms of the innate perceiving skills at early ages of human during naturalistic music listening.**

***Index Terms*—Preterm infants, dynamic functional connectivity, reliable component analysis, functional near-infrared spectroscopy, naturalistic music listening.**

I. INTRODUCTION

THE mystery of music has attracted numerous researchers trying to explore the origin of music and its power over human. Darwin noted that human faculties for music “must be ranked among the most mysterious with which (man) is endowed.” [1]. Previous scholars suggested that music has a specific cognitive function to embody abstract thoughts [2], and the pitch and rhythm contained in music can trigger emotions [3]. What’s more, the biological power of music [4] has effect on the cognitive abilities of human exhibiting the improvement of cognition and learning capacity [5]. Music perception is a complex procedure. However, people have been voluntarily or involuntarily exposed to and influenced by a great deal of music from infancy. To explain the distinctive ability of human in perceiving music, it is necessary to reveal the newborns’ ability to perceive music. Fetus and newborns are exposed to a limited range of sound stimuli, including sounds from the mother (such as heart beats, breathing and speech) and sound from external world filtered through the womb, who do not have a systematic learning process of the music. Preterm infants, as a special population, have prematurely terminated their typical developmental trajectory in the maternal uterus due to diverse known or unknown factors. Additionally, they still evolve in striking developmental brain changes. Therefore, to explore the innate musical perceiving ability which can be generalized to all human beings, infants with preterm birth should be employed as subjects due to their possibly compromised brain maturity. The investigation of the auditory system of premature infants is beneficial to the development of multidisciplinary studies, including the revealing of the biological basis of music and providing insight into the music-specific processing skills at an early age of human [6].

Researches into infants’ ability to perceive music began in 1970s. These researches in infants during exposed to music have gone through three stages [7]: starting with the researches in studying heart rate variability, and then the behavior response by independently turning his/her head

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to the directions of his/her interesting music, and the neural response that developed to date. The study on the neural response expands the research scope in terms of the populations from infants to newborns, resolving the underlying problems such as the inaccessible or unreliable behavior response of the newborns. According to the investigation of neural response to music stimuli based on the event-related paradigms, it revealed the ability of newborns to perceive music [8], [9]. And newborns showed an adult-like music processing of pitch relations representing a hemispheric functional asymmetric [9], [10]. Therefore, the investigation of the neural response could explore the neural basis of the auditory system.

So far, the investigation of the auditory functions was mainly based on the task-related state. The task-related state is designed to finish the artificial predefined tasks (i.e. block design, event-related design, and mixed design experiments) [11]. The task-related studies with discrete events have revealed the fundamental insight into functional specialization in the brain. However, this approach delivers with sparse and repetitive events, which do not resemble the complexity and dynamics of stimuli and behaviors exposing in real life (i.e., low ecological validity) [6]. However, the investigation of the complex and dynamic cognitive process is a great challenge for research in the field of brain science.

Previous studies have shown that functional Near-Infrared Spectroscopy (fNIRS), with good portability, high comfort, relatively high spatial and temporal resolution, and relatively high tolerance to exercise, is more suitable for the study of brain function in the natural environment and special population [12]–[15]. Our previous study with fNIRS provided the evidence that preterm infants have the capability to perceive music features [16] and that music could achieve the effect of calmness and relaxed state correlated with lower brain activities [17]. And the prefrontal and temporal regions were found to be evoked by music using fNIRS [18], [19]. However, most auditory studies with fNIRS were limited to exploring the activation patterns or distinguishing different auditory modalities [18]–[22] lacking in investigating brain functions in network level, especially dynamic brain network. It is helpful to reveal the functional mechanisms of the brain through studying the spatial patterns of the dynamic functional brain networks during naturalistic stimuli. Crucially, naturalistic stimuli overcome the challenges existed in resting state or task-related task studies [6]. The naturalistic stimuli show a strong consistency in intra- and inter-subject correlation, and characterize by a test–retest reliability of neural activity and functional connectivity during natural viewing and listening conditions using fMRI and EEG signals [6], [23]–[26]. However, considering the low temporal resolution of fMRI and the strict requirement to the experimental environment, the fMRI study of brain function in task state may lead to the lack of temporal information and the absence of the properties of natural scene. The attributes of EEG with poor spatial resolution [15] and susceptible to motion artifacts [27] limit the application of EEG in investigating brain networks in natural environment. It is also worth noting that the low signal-to-noise ratio (SNR) makes it difficult to process the signals acquired in the natural state. Scholars used original EEG signals when subjects watched the same movie to find the component with the strongest correlation within subjects, which was called reliable component analysis (RCA) [24]. The RCA approach will not be affected by the low SNR in the natural state. Additionally, the extracted spatial filter using RCA can reflect the brain states corresponding to the concurrent involvement of the brain regions within or across subjects.

Therefore, in this study, we combined the advantages of fNIRS application in the natural scenario with the original brain system without postnatal training to capture meaningful functional brain patterns during natural listening music in preterm infants. The synchronized functional brain activities of different subjects when they experience the same stimulus can be extracted from the dynamic functional connectivity time series using RCA. The analysis of the brain network using RCA reduces the interference caused by the occurrence by chance. Additionally, it is helpful to reduce the individual differences within subjects, and to capture the shared brain states across subjects. This study provides a new way to investigate the neural basis of preterm infants involved in the same musical processing by revealing the characteristics of the brain networks and the relationships between the networks.

II. MATERIALS AND METHODS

A. Experimental Design and Data Collection

1) Participants: Ten preterm infants (gestation age: 34.5 ± 1.0 weeks, gender: 8 boys, 2 girls, weight at birth: 2231 ± 331 g) with stable physical signs were recruited from the Children's Hospital of Fudan University in this study. This study was reviewed and approved by the ethics committee (approval number: 2017-235), and informed consent was obtained from the subjects' parents. Before the experiment, preterm infants were screened by experienced neonatologists based on the inclusion and exclusion criteria. The inclusion criteria were: (1) gestation age within 32-37 weeks; (2) 1-min and 5-min Apgar score ≥ 7; (3) pass the automated auditory brainstem response screening (AABR). The exclusion criteria were: (1) with nervous system disease or intracranial hemorrhage; (2) with severe congenital disease; (3) with the treatment of apnea or mechanical ventilation treatment.

2) Experimental Paradigm: The experiment began 30 minutes after the subjects receiving formula feeding. The preterm infants were in the supine position in incubators with appropriate temperature and humidity. Previous studies have proved that the ability to perceiving music originates during the third trimester of gestation [28] and preterm infants are capable to perceive and remember sound information [8], [29]. Therefore, a 3-minute music clip from Mozart Sonata for Two Pianos in D Major, K.448 (Mozart K.448), performed by Karl Ulrich Schnabel and Helen Schnabel was selected for the experiment. All the subjects were exposed to the same musical clip. During the whole experiment, the ambient noise was controlled as much low as possible to ensure that the background noise in the incubator was below 40 dB, and the sound pressure level of the music near to two side ears of

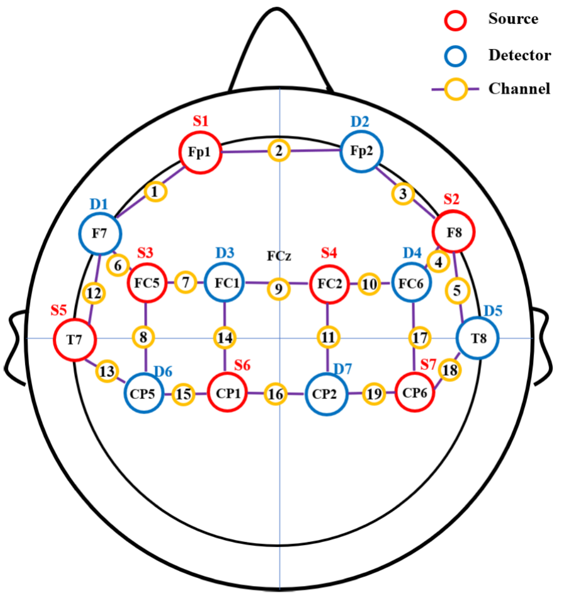


Fig. 1. Layout of the probes of fNIRS. The red circles represent light sources, blue circles denote detectors, and the purple lines with yellow circles represent the channels formed by each pair of light source and detector.

the subject was controlled below 65 dB. The whole procedure of the experiment lasted for 23 minutes containing 10-min pre-resting, 3-min music stimulus, and 10 post-resting states.

3) fNIRS Acquisition: According to the neurovascular coupling mechanism, changes in neural activity during stimulation can be reflected by changes in oxygenated and deoxygenated hemoglobin concentrations. In this study, the brain activity in response to the music stimulus was recorded by the NIRScout measurement system (NIRx Medical Technologies, LLC., USA), which was based on continuous wave techniques with 8 LED sources and 8 detectors at the wavelength of 760 and 850 nm. In this study, 7 sources and 7 detectors were used to form 19 channels in total. The layout of the probes was based on the international 10-10 system covering the frontal, temporal, and parietal regions. The layout of the probes was shown in Fig.1. The source-detector distance selected in this study was 3 cm, which is in line with previous neonatal studies in investigating auditory brain functions [21], [30]–[32]. In order to prevent the probes from damaging the scalp of the subjects, a silicone pad was attached at the front of each probe. The fNIRS sampling rate was automatically set to 8.9286 Hz by the acquisition system. Music and trigger signals were controlled by E-prime software (Psychology Software Tools, Sharpsburg, PA), which ensured the synchronization between fNIRS signal and music and that the fNIRS signals of different subjects were aligned at the beginning of the music. After each experiment, the probe and other experimental supplies were strictly disinfected to avoid indirect contact infection. The whole experiment process was accompanied by professional nurses.

B. Methods

1) fNIRS Pre-Processing: The light signals received by the fNIRS detectors reflected the fluctuation of cerebral oxygenation. The signals were then converted into changes in the oxygen hemoglobin (HbO2) and de-oxygen hemoglobin (HHb) concentration based on the modified Beer-Lambert Law using the nirsLAB software (NIRx Medical Technologies, USA). The relative changes of fNIRS signals in relation to the baseline were obtained by minus the average value of the 20 seconds before the music stimulus. Previous studies have shown that the changes in HbO2 were more sensitive to brain activity during task performance. Therefore, only the HbO2 signals were recruited in this study. A band-pass filter (0.01-0.3Hz) was then performed to remove the interference of low-frequency drift and high-frequency physiological interferences such as the oscillations of cardiac activity, respiratory information, and Mayer waves [33]. Additionally, the validity of fNIRS signals were checked using our previous proposed method by calculating the correlations between music features and fNIRS signals [16]. The detailed procedure and results are presented in Supplementary A.

This study mainly focused on investigating the dynamic brain functional networks during naturalistic music listening on preterm infants using the dynamic brain functional connectivity (dFC). RCA method [24], [34] was carried out on the dFC time series across subjects, and the dynamic functional networks with the highest correlations across subjects were obtained during subjects receiving the same music stimulus. Fig.2 depicts the schematic diagram of the analysis procedure of dynamic functional brain networks using RCA.

2) Dynamic Functional Connectivity: The analysis of functional brain networks began by calculating dFC time series using sliding window correlation analysis which was the prevalent method utilized in the field of neuroimaging [35]. The analysis procedure is shown in Fig.2 (a). The fNIRS data were the same as the duration of the music (3 minutes) with a sampling rate of 8.9286Hz, forming a final length of 1607 sampling points in each subject. According to the experience of dFC calculation using fMRI [25], the dFC time series in this study were calculated by 30 s windows with 120 ms window step (the duration of one sampling point) and thus resulted in 1341 windows. Pearson correlation analysis was used in each window to calculate the connectivity between each pair of channels. Therefore, the time series of $C_{19}^2 = 171$ pairs of dynamic functional connectivity was obtained.

3) Reliable Component Analysis: In this study, the RCA method was adopted to analyze the continuous dFC time series, so as to extract the components corresponding to the strongest correlation of the functional connectivity across subjects. The premise of this method was under the hypothesis of the existing EEG and fMRI studies that when subjects were exposed to the same musical stimulation, similar neural activity and highly consistent dynamic connectivity would be generated [24], [25]. The procedure of the RCA in terms of dFC time series was shown in Fig.2 (b).

In the calculation process of RCA, the correlation between the continuous time courses of functional connectivity and the data of the second listening to music was firstly analyzed [24]. In this study, the second listening data were from different subjects who listened to a piece of common music. And then the optimization process was reduced to the eigenvalue solution by maximizing the covariance of multiple records,

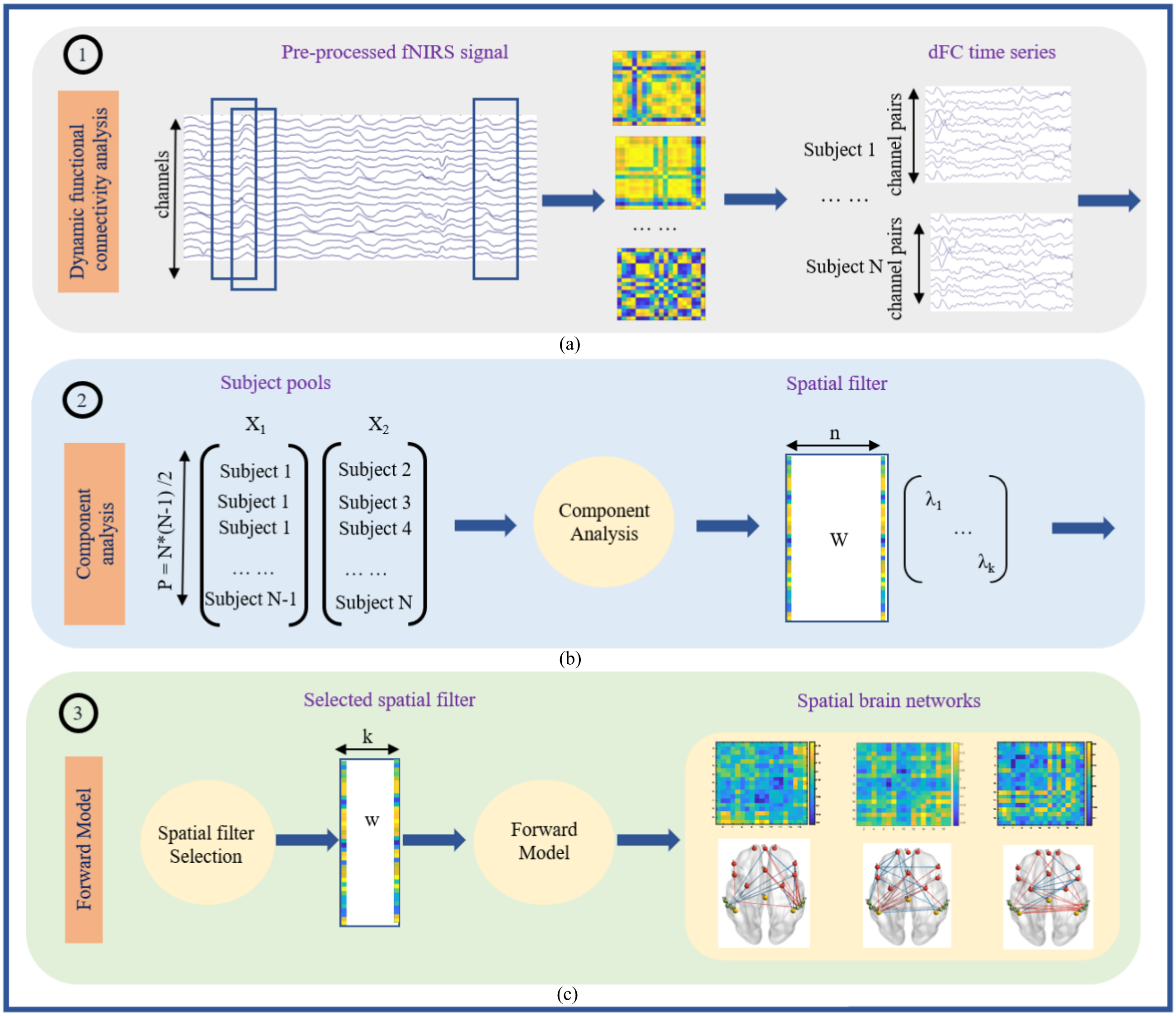


Fig. 2. The schematic diagram illustrating the fundamental processing pipeline. (a) The processing pipeline applied on each subject data from fNIRS signal to dynamic functional connectivity series. (b) RCA applied on the group-level of dFC signals. (c) The 3-dominant task-related spatial brain networks extracted by Forward Model.

resulting in the eigenvalues sorted in descending order (containing n component) and their corresponding eigenvectors representing linear weights among nodes (i.e., channel pairs). The eigenvector w as the spatial filters projected the data of all subjects onto a common space such that the obtained projections manifested maximal inter-subject correlations across the subject pools. The first three eigenvalues and their corresponding eigenvectors were selected for further analysis in this study according to the previous studies [24]. The RCA method was performed using a publicly available MATLAB implementation in this study (*https://github.com/dmochow/rca*). The mathematical details of the RCA method can be found in Supplementary B.

According to the selected spatial filter W obtained by the above RCA method, the original dFC across the subject pools was transformed from the node-by-time matrices to component-by-time matrices. For instance, the original dFC time series $x_i \in \mathbb{R}^{D\times T}$ in subject i was projected to $y_{ik} = x_i * w_k$ $(i = 1, 2, \ldots, N, k = 1, 2, 3)$, where D is the number of nodes and T represents the number of time samples of the dFC, and y_{ik} represents the dFC projection corresponding to component w_k in subject i. The resulting dFC projection is denoted by ReDFC in this study.

Previous studies have clarified the significance of the selection of the sliding window length in the calculation of dFC [25]. In addition to the 30s window length, the dFC at the window length of 15 s and 60 s were also calculated to compare the influence of different window lengths on the results of RCA. For each sliding window length, the RCA method was executed with the same process as described above.

4) Inter-Subject Correlation Analysis: The inter-subject correlation analysis of the ReDFC time series was conducted to obtain the fluctuations of the inter-subject correlation over time which corresponded to the alter of the music stimulus. In the calculation of the inter-subject correlation among N subjects, the one-against-all approach was executed whereby the time series of one subject were correlated with the averaged time series of the remaining N-1 subjects [25], [36]. Thus, an inter-subject correlation (ISC) time series is generated for each ReDFC component in each subject. In order to intuitively represent the fluctuation of ISC among subjects over time, we used the same sliding window method but with a different window size (window size 5 s and step length 0.12 s) to perform the above steps. In this study, the number of subjects was ten, and the above steps were repeated ten times to obtain the ISC corresponding to the ReDFC in each subject. For each ReDFC component, the ISC r-map was transformed into Fisher's z-map, and the averaged ISC z-map of all the subjects was used to reflect the fluctuations of the correlation across subjects.

Additionally, the phase difference between the first two ReDFC components was analyzed to assess the transient relationship between the time courses of the ReDFC components. In order to get the characteristics of the group, the mean values of ReDFC among the subjects were calculated and denoted by $\bar{y}_k(k = 1, 2)$. Hilbert transform was performed to quantify the instantaneous phase of each averaged ReDFC time series and the phase difference between them was extracted [37]. Specifically, the complex signal of ReDFC $\hat{\bar{y}}(t)$ was obtained by Hilbert transform:

$$\hat{\bar{y}}(t) = hilbert(\bar{y})(t) \tag{1}$$

And then the instantaneous phase φ(t) of the time courses of $\bar{y}(t)$ was obtained:

$$\varphi(t) = angle(\hat{\bar{y}}(t)) \tag{2}$$

The phase difference between the two ReDFC time series was defined as:

$$\Delta\varphi(t) = \varphi_1(t) - \varphi_2(t) \tag{3}$$

where $\varphi_1(t)$ and $\varphi_2(t)$ denote the instantaneous phase of the first and second ReDFC components, respectively. The phase difference between the two components provided a comprehensive understanding of the interaction of the brain networks corresponding to the ReDFC components varied over time.

5) Forward Model: The scalp projection of the extracted components w yielded by Eq.(S.5) (refering to Supplementary B) was obtained through the forward model, and thus the spatial and temporal properties of dFC could be better explained. The illustration of the forward model is shown in Fig.2 (c). The visualized topographies of the resulting components were proposed by Parra et. al. [38]:

$$A = RW(W^T RW)^{-1} \tag{4}$$

where W is the weight matrix whose columns denote the optimal spatial filters produced by RCA. $R = R_{11} + R_{22}$ represents the auto-covariance of the subject pools. A represents the forward model whose columns denote the scalp projections of dFC corresponding to the spatial filters. According to the anatomical location of each node, the corresponding brain network topography can be obtained (shown in Fig.2 (c)).

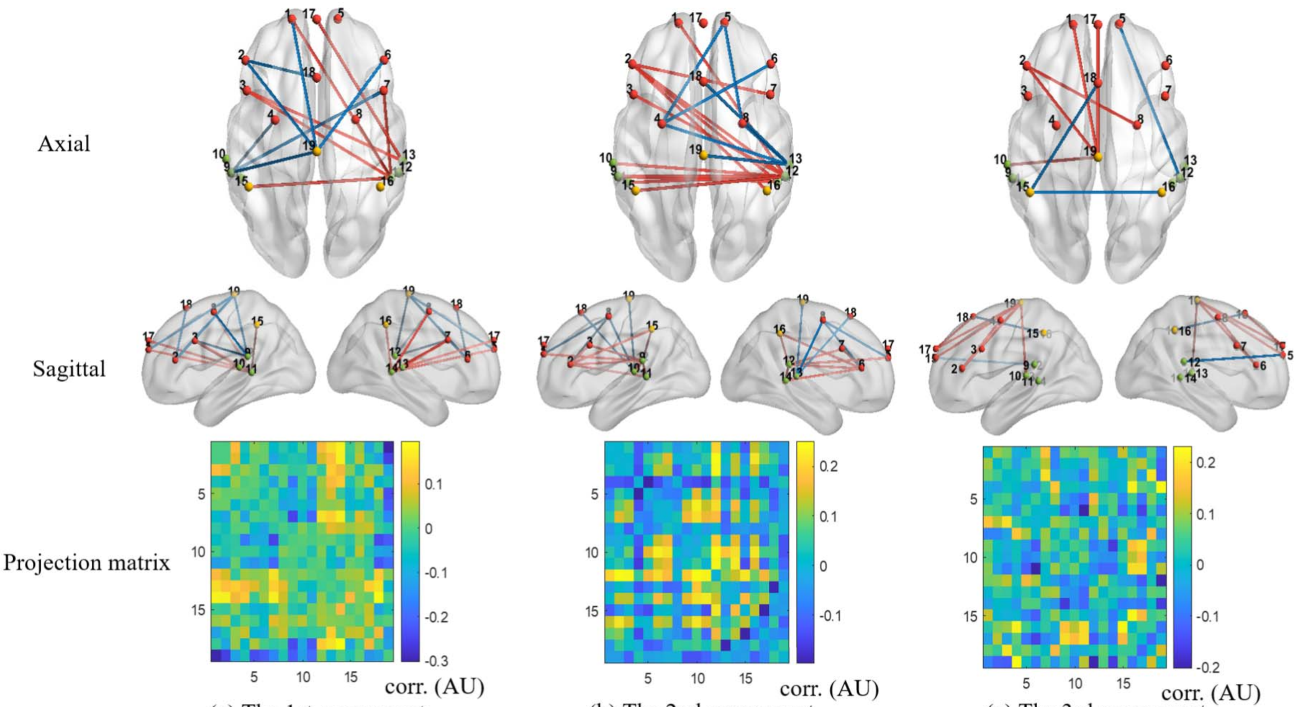
6) Statistical Analysis: The statistical significance of each ISC was assessed through a permutation test approach [24], [26]. The correlation values under the null hypothesis were computed by the correlations of two surrogate records from two subjects. The original dFC records were segmented by 5-s windows, and then the randomly scrambled order of the windows yielded the surrogate data. The component analysis was repeated 100 times over the surrogated data. The statistical significance level was $p < 0.01$. The multiple comparisons were corrected by the False Discovery Rate (FDR) [39]. All the statistical analysis was performed using MATLAB (MathWorks^{TM} Inc., Massachusetts, USA).

III. RESULTS

A. Components of the Inter-Subject Correlations

We began by exploring the spatial patterns which were extracted by the RCA process. According to the inter-subject reliable component analysis, the optimal spatial filter was extracted which maximized the inter-subject correlations across the dFC time series. And then the spatial patterns of the brain functional connections corresponding to each spatial filter were obtained through the forward model, where the elements in each column in A represent the activated connection nodes in the brain networks.

The spatial structure of the brain functional connectivity networks that reflects the first three strongest inter-subject correlations extracted by RCA is shown in Fig.3. From the first three extracted brain networks, a synchronized functional connectivity is exhibited between and within multiple brain regions. The dominant connections are found between the temporal region and other brain cortex (i.e., frontal, and parietal lobes). In Fig.3 (a), extensive synchronizations are found between the right temporal cortex and frontal cortex, while the fluctuations of the fNIRS signals between the left temporal region and frontal region are not consistent. In the connection between right temporal and bilateral frontal regions, the involved the temporal regions include the posterior part of superior temporal gyrus (corresponding to channel 13 and 14), and the involved frontal region incorporate the inferior frontal gyrus (corresponding to channel 3 and 7), the superior frontal gyrus (corresponding to channel 8), and the prefrontal cortex (corresponding to channel 1 and 17). In Fig.3 (b), a more sophisticated the functional connectivity between brain regions are represented. It shows a pattern showing the functional synchronizations between the right temporal cortex and the contralateral inferior frontal gyrus (corresponding to channel 2 and 3) which is similar to the first brain network, as well as synchronizations between the bilateral temporal regions. In Fig.3 (c), the primary somatosensory cortex (corresponding to channel 19) shows synchrony with the prefrontal lobe and the left inferior frontal gyrus (corresponding to channel 2), while there is no synchronization between the bilateral temporal regions and the frontal region. Overall, the spatial structure of the brain networks in terms of functional connectivity across brain regions, it exhibits



(a) The 1st component (b) The 2nd component (c) The 3rd component

Fig. 3. Spatial distribution of the component topography extracted by RCA method. Each column represents the spatial structure of the corresponding component. The first two rows represent the 3D model of the brain spatial maps from the axial and sagittal positions, thresholded with 70% of the maximum connection strength for visualization. The nodes with different colors represent different brain regions: red for the frontal cortex, yellow for the parietal cortex, and green for the temporal cortex. The lines between different nodes indicate the strength of functional connectivity between channels, where the red lines indicate strong synchronization between two channels, and the blue lines indicate desynchronization between channels. The third row shows the matrix representation of the brain networks. The values of each element in the matrix correspond to the results of the spatial filter passing through the forward model.

the functional left- and right-hemisphere lateralization of the frontal and temporal cortices, respectively, as well as the synchronizations between bilateral temporal cortex.

B. Interactions Between the Brain Networks

In this paper, the functional responses of the brain to music can be reflected from two parts: the fluctuation of the ISC time series and the phase difference between ReDFCs. The investigation of the two parts helps to interpret the principles of the cooperation of auditory brain networks underlying the perception of music. Firstly, the ISC time courses represent the fluctuation of the consistency of ReDFC time series across subjects associated with the changes of the musical characteristics. Secondly, since the spatial structure of brain networks obtained by the forward model A is corresponding to the optimal spatial filters extracted by the component analysis, the time-varied phase difference between ReDFCs denotes the interactions of the corresponding brain networks.

The resulting population ISC time series corresponding to the three ReDFCs are shown in Fig.4 (a). In each ISC, the time-varied correlation coefficients were observed, and the fluctuations of the ReDFC showed strong consistency among subjects at certain time duration. One possible explanation may be that the significant correlations stem from the specific properties of music. We quantified the strength of the fluctuations of each ISC using the zero-crossing method. According to the zero-crossing number shown in Fig.4 (b), the fluctuation of the correlation among subjects was more obvious in the second and third ISC. The reason may be that the corresponding eigenvalues in RCA were sorted in descending order, resulting in the decrease of the correlation between subjects. Additionally, this fluctuation may also result from the spatial structure of the brain network, which is more sensitive to certain musical features.

The interaction of the extracted three brain networks contributes to the perception of music. The brain network is in a dynamic process of formation and dissolution with the change of music features over time. To explore the relationship between ReDFC components during the perception of the musical stimulus, the transient phase of the first and second ReDFC components was calculated to demonstrate the interactions of the brain functional networks. The mean values of the first and second ReDFC components reflecting the population characteristics of the functional connectivity are shown in Fig.5 (a). Fig.5 (b) is the polar histogram of the instantaneous phase difference between them. The results showed a phase lead of $60-80°$ for component 1 vs. component 2, indicating the cooperative characteristics of the brain functional networks in terms of the dynamic functional connectivity.

C. Effects of the Sliding-Window Length

Although the selection of window length is very important in the calculation of dynamic function connectivity, previous studies have not given an optimal selection range of window

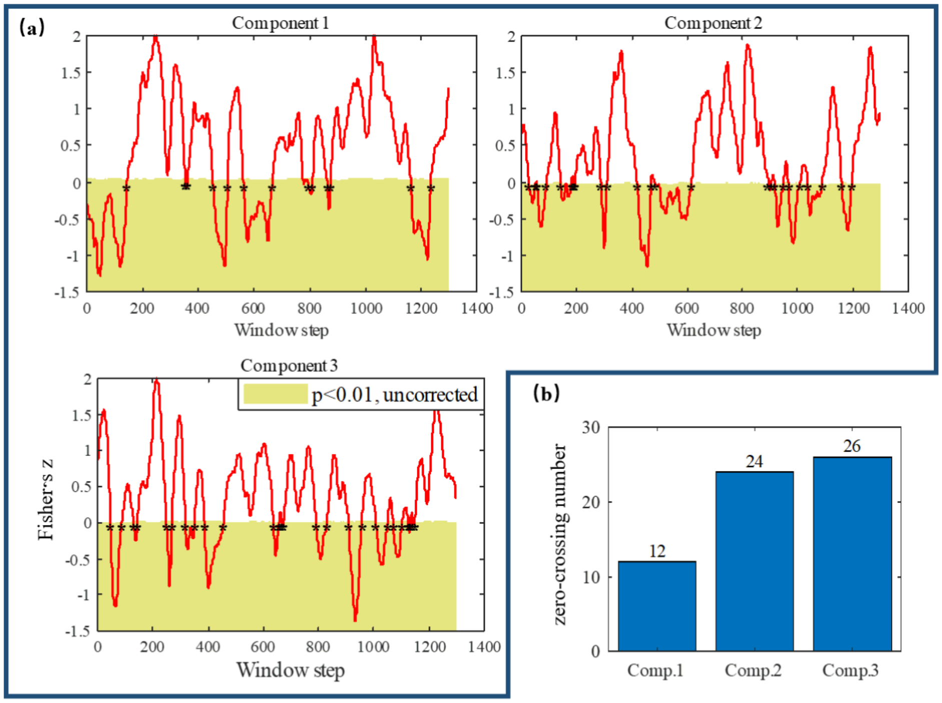


Fig. 4. Results of the inter-subject correlation. (a) The resulting population ISC time series. Note that the values of the population ISC time series are the averaged *z*-value across all the subjects. The solid red line represents the mean value of ISC across subjects, and the yellow shaded area indicates the correlation level require to achieve significance at $p < 0.01$ level. (b) The histogram of the zero-crossing number of the ISC time series.

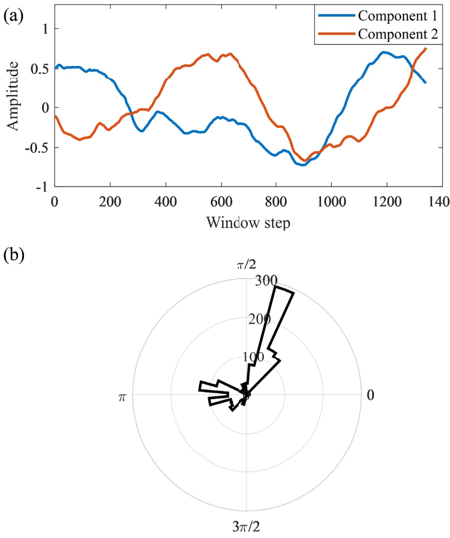


Fig. 5. Relationship between the first two ReDFC components. (a) The averaged ReDFC across subjects, where the solid blue and red lines indicate the first and second ReDFC components, respectively. (b) Polar histogram of the instantaneous phase difference between the first two ReDFC components. Thirty-six 10-degree bins cover the entire angle range of 0 – 360°.

length. Therefore, in this study, the dynamic functional connection was calculated at the window lengths of 15s, 30s, and 60s, respectively.

The ReDFC components yielded by component analysis at three different window lengths are shown in Fig.6 (a). According to Fig.6 (a), the variability of the ReDFC time courses was larger at the 15s window. The short window length results in rapid changes in the dynamic connectivity, such that it reduces the consistency among subjects. In contrast, the ReDFC component obtained at the window of 30s is relatively smooth, which increases the correlation between subjects, partly due to that a longer window reduces the impact of random factors (e.g., noises). However, the time series of dynamic connectivity obtained at 60s window length becomes too smooth, which makes the average trend among subjects become insignificant, such as the third component at 60s window.

Additionally, we compared the spatial maps formed by the spatial filter corresponding to the first ReDFC components with three different window lengths. The activation patterns under three window lengths are basically the same, which shows strong connectivity between temporal cortex and frontal cortex, as shown in the symmetrical areas with red blocks in Fig.6 (b). Fig.6 (c) shows the mean values of the correlations of the ReDFC time series across subjects with different window lengths. The correlation among subjects in a short window was reduced due to the high variability of the dynamic connectivity, which was consistent with the results in Fig. 6 (a). For the comparison of the three ReDFC components, the first component had the highest correlation among subjects, which was in line with the properties of component analysis that the maximum eigenvalue corresponds to the maximum correlation of the inter-subject signals. Under the three sliding windows, the correlations of the three components are successively reduced, which consistently shows the largest value in the first component. However, the correlation of the third ReDFC component was the worst at the 60s window.

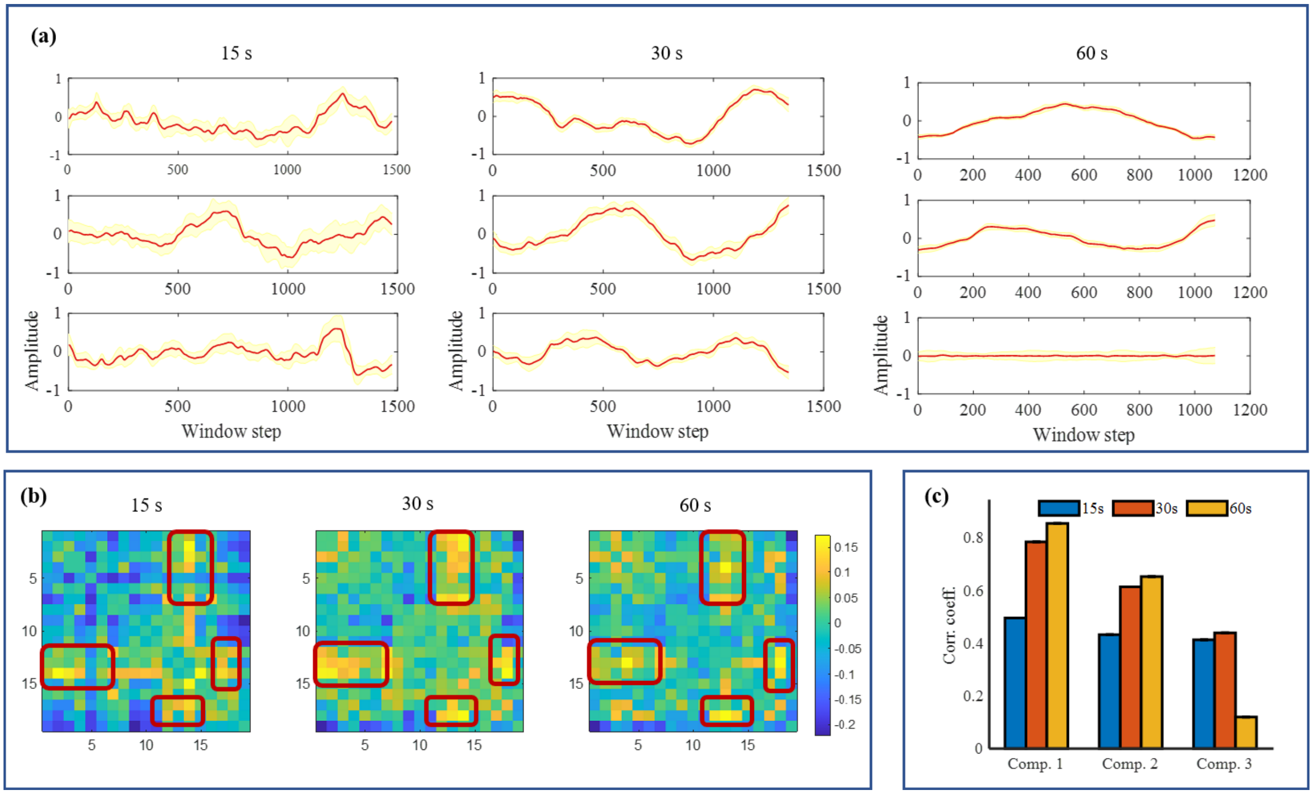


Fig. 6. Comparisons of the resulting components in different sliding-window length. (a) The time series of the ReDFC components extracted by RCA under 15s, 30s, and 60s window lengths. The solid red line represents the averaged ReDFC time series across subjects and the yellow shade represents the standard deviation of all the subjects. (b) Spatial distributions under different window lengths. Consistent activation patterns are shown between temporal cortex and frontal cortex under the three window lengths, marked with the red blocks. (c) The histogram of the averaged correlations of the ReDFC across subjects.

IV. DISCUSSION

In the current study, we proposed to investigate the inter-subject correlations of dynamic functional connectivity during naturalistic music listening using component analysis to extract meaningful dFC patterns in preterm infants. The maximum inter-subject correlations of the dFC time series extracted by RCA reflect the shared spatial brain networks in response to the common music stimuli. The results showed that the auditory brain networks in preterm infants during Mozart music perceiving involve a wide range of brain connections. These connections maybe not have been found in previous studies on preterm infants [9], [18], which reveals a new perspective that a large number of brain regions are involved in the processing of musical information and that multiple brain networks associated with perceiving musical features cooperate together during listening to music in preterm infants. Additionally, the validity of the component analysis underlying dynamic functional connectivity was verified under different sliding windows. The consistent activation patterns generated from the spatial filters reveal the robustness of the dFC-based RCA method.

A. Emerged Large-Scale Brain Networks

The perception of music involves the participation of the auditory cortex and multiple brain regions to complete the complex process, including the extraction of music information [9], [40], memory storage [29], and the interaction of the emotional systems [41]. The properties of music in the absence of a concrete description of the content make the perception of music more abstract. Previous studies have shown that the processing of acoustic stimuli is primarily carried out in the right hemisphere in adults [42]. Additionally, there also has evidence that the decoding of complex musical structures in musical information takes place in bilateral hemispheres [43]. In this study, the extracted three brain network patterns by RCA found that the process of listening to music in the population of preterm infants involves the functional connectivity between the temporal cortex and frontal cortex, as well as the functional synchronizations between the bilateral temporal regions. Compared with the previous studies which only reported the activation patterns (i.e., activated temporal or prefrontal regions) [18], [21], [44], this study presumably illustrates that the perception of music involves a wide range of functional connections in both hemispheres in preterm infants at brain network level. Therefore, it can reveal more abundant information of auditory brain networks using the inter-subject correlation method based on dynamic functional brain networks in naturalistic environment.

B. Physiological Significance of Dynamic Brain Networks

The auditory brain networks extracted in this study have important physiological significance and provide substantial insight into the interpretation of music perception in preterm infants at the brain network level. In the first two extracted brain networks, the functional connectivity between the right temporal and the frontal regions (including the prefrontal cortex, superior frontal gyrus, and inferior frontal gyrus) was found. A large number of studies have shown that music has the ability to evoke powerful emotions, which is regulated by the prefrontal cortex [45], and that the inferior frontal gyrus is responsible for processing musical structure [46]. In the present study, the synchronous activation of temporal and prefrontal regions may be partly related to the elicited emotion by Mozart music in preterm infants. Additionally, existing studies have shown that the activation of the left frontal lobe is related to positive emotions [47] and that the prefrontal regions are responsible for higher-order cognitive functions. It presumably indicates that preterm infants have the capability to perceive music, and meanwhile the Mozart music may also evoke the changes in the positive emotion. The first brain network extracted in this study, showed functional connectivity between the right temporal lobe and the inferior frontal gyrus, which is consistent with the previous studies showing that the inferior frontal gyrus are activated during listening to music or perceiving abstract structural information [48], [49]. Since language and music share similar syntactic structures [50]–[52], the functional connectivity involving the inferior fontal cortex and the bilateral temporal cortex in the second brain network presumably prove that the intimate links between music and language is established in human at early ages. Moreover, previous study has shown that the connection between primary somatosensory cortex (located in postcentral gyrus) and the frontal area is thought to be related to cognitive functions, such as control [53]. The functional synchronizations between the primary somatosensory cortex and the frontal cortex in the third brain network may be partly related to the motor activity and sensory.

Additionally, by analyzing the inter-subject correlations of the three ReDFC components among the preterm infants, we speculated that the fluctuation of ISC among the subjects presumably correspond to the musical characteristics that changed with time. We also found that the brain networks corresponding to the first component were more robust, while the brain networks corresponding to the second and third components were more sensitive to the fluctuation of musical characteristics. The phase difference between the first and the second ReDFC components by calculating the instantaneous phase was found to remain at a fixed level, indicating that the brain functional connectivity networks corresponding to the two components represent a dynamic collaborative relationship when receiving music stimulation, and different brain functional networks had their specific functions in perceiving music in premature infants. From the component topography and the empirical evidence of the functional specializations of the brain, we infer that the first brain function network is responsible for the decoding of the complex musical information, the second brain function network involves the functions of music comprehension, emotion generation and language processing, and the third brain function network is responsible for memory and sensory.

The investigation of functional brain networks captured by fNIRS using RCA provides a new approach to exploring the cognitive state of functional brain synchronization during naturalistic stimuli in preterm infants. Critically, the coordination of the brain networks may be partly related to a sophisticated process of perceiving musical information in preterm infants. This provides further evidence that the newborns' ability to perceive music is the innate skill without training. The music-related skill may be associated with human genes, likely the results of the natural evolution during the time of our ancestors to adapt for survival or to facilitate human relationships. The investigation of the functional response of brain to naturalistic stimulation provides new insights for the field of neuroscience to understand the unique neural mechanisms of human beings. In addition to revealing the underlying mechanisms of auditory system, the abnormalities in auditory brain functional networks, such as changes in functional connectivity and the phase changes between brain networks, may also provide a possible biomarker for the diagnosis for neurological diseases in the developing brain.

C. Window Selection Considerations

The selection of sliding windows will directly influence the result when calculating dynamic functional connectivity. A previous fMRI study has clarified that there is a trade-off between the temporal resolution and estimated accuracy during the calculation of dynamic functional connectivity [26]. A shorter or longer time window would provide a better temporal resolution of the dynamic functional connection while containing more noise. However, due to the small number of sample points in the time window, the estimated time series of dynamic functional connectivity contain more noise, which eventually leads to the decrease of the correlation across the subjects. In the current study, the dynamic functional connection calculated by the 15 s sliding window has a low correlation among subjects after RCA, whereas in the case of the 60 s sliding window, the increase of inter-subject correlation is accompanied by the decrease of the temporal resolution. The 30 s sliding window can achieve the trade-off balance. Overall, regardless of the connectivity projection matrix obtained from the smaller sliding window or the larger sliding window, it consistently shows the synchronization of the right temporal lobe and frontal lobe connections in the first ReDFC component, suggesting the robustness of the brain functional network extracted from dynamic functional connections using RCA method.

D. Limitations

fNIRS is easy-to-use in the naturalistic environment and efficiently reflect the activation of the cerebral cortex. However, two limitations in this present study should be noticed. First, regarding the measuring techniques, fNIRS has limited measurement depth and spatial resolution compared to fMRI. Therefore, due to the limitations of the fNIRS technology, functional connectivity in the cerebral cortex can only be detected. The functional connectivity information of deep brain regions, such as basal ganglia involving in auditory processing [54], is not available. Additionally, the obtained fNIRS signals are confounded by extracranial signals.

Future studies may consider using multi-distance channels or building models to remove the interference of superficial components. Second, we only measured frontal, parietal, and temporal cortex, excluding the occipital regions to prevent pressure ulcers in preterm infants. However, previous studies have shown that the occipital region involves synesthesia during music listening, enriching musical information [55]. Considering all the above, studying the whole brain regions using fNIRS brings great challenges to future studies. Despite these limitations, fNIRS still has great potential for clinical application and brain science research.

V. CONCLUSION

In the current study, we explored the auditory brain networks and revealed the underlying neural basis of the innate music perception skills in preterm infants. The activation of the brain regions involving the perception of Mozart music was analyzed at the brain network level in preterm infants. The dynamic functional connectivity components with the strongest correlation across the subjects were calculated by RCA, and the spatial topography corresponding to the optimal spatial filter was obtained. The fluctuation of the ISC time series, as well as the phase difference between the first two ReDFC time series, demonstrated the cooperation of the auditory brain networks during music listening. The inter-subject based approach may provide a complementary approach to understanding the mechanisms of the brain in terms of dynamic functional connectivity and exploring the functional collaboration of the auditory brain networks in preterm infants. our findings may also provide a physiological basis for understanding the indispensable auditory neural basis of human evolution and the relationships between music and human evolution.

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