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ORIGINAL PAPER

Preterm Modulation of Connectivity by Endogenous Generators: The Theta Temporal Activities in Coalescence with Slow Waves

Azeez Adebimpe[1,2] · **Laura Routier**[1,3] · **Fabrice Wallois**[1,3]

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Abstract

The neuronal activity of the preterm brain is characterized by various endogenous activities whose roles in neurodevelopmental maturation processes have not been fully elucidated. The preterm EEG is characterized by discontinuities composed of short bursts of activity with dominant low frequencies. One of the earliest endogenous activities is the theta temporal activity in coalescence with slow waves (TTA-SW), which appears at 24 to 32 weeks of gestational age (wGA). The present study investigated the influence of TTA-SW on the spatial organization of the early preterm brain network. To achieve this objective, High-Density EEG data were recorded from preterm infants (29–32 wGA) and functional connectivity (FC) was estimated from the scalp EEG. TTA-SW, particularly in the theta band, induced increased FC between left temporal and left frontal areas and between left temporal and parietal areas with TTA-SW at the left temporal region, while FC was limited to the right temporal regions in the case of TTA-SW at the right temporal region. Regardless of the lateralization of TTA-SW, long-range FCs were observed between left frontal to left parietal areas, suggesting that these regions, together with the temporal region, provide a basis for coherent neuronal activation across distal cortical regions. TTA-SW dynamic features showed that brief phases of TTA-SW had an impact on both local and whole brain network organization, supporting the importance of TTA-SW as a biomarker of brain development.

Keywords Temporal theta activity · Preterm · EEG · Functional connectivity · Development

Introduction

There is growing interest in improving our understanding of the complexity of the neurodevelopmental dynamics of preterm brain networks and their functional connectome (Fransson et al. 2007; Omidvarnia et al. 2015). During preterm brain development, dynamic interactions between the cortical subplate and the developing cortical plate (Kostovic and Judas 2010) are driven endogenously by thalamocortical connections (Kostovic and Judas 2010). Between 31 and 34 wGA, the cortical plate develops into six cytoarchitectonic layers and these layers are associated with the establishment of thalamocortical circuits. This structural substrate is essential for the transition from endogenous spontaneous processing to sensory-driven functioning (Kostovic and Judas 2010). This sensory-driven and endogenously generated neural activity is important for wiring neural circuits that participate in the complex cortical functions of adulthood (Penn and Shatz 1999).

Electroencephalographic (EEG) patterns observed in preterm infants are very different from those observed in term neonates, young children and adults EEG (André et al. 2010). EEG data from very preterm neonates (up to 24 wGA) consist of long periods of low-amplitude activity interrupted by bursts of high-amplitude activity at multiple frequency bands, ranging from infraslow (Vanhatalo et al.

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✉ Azeez Adebimpe
adebimpe@upenn.edu

[1] INSERM, UMR 1105, Research Group on Multimodal Analysis of Brain Function, University of Picardy Jules Verne, 80036 Amiens Cedex, France

[2] Department of NeuroPsychiatry, University of Pennsylvania, Philadelphia, PA 19104, USA

[3] INSERM, UMR 1105, Pediatric Nervous System Functional Investigations, Amiens University Hospital, Avenue Laennec, 80054 Amiens Cedex, France

2004) to higher frequency activities (Tolonen et al. 2007; Vecchierini et al. 2007; André et al. 2010). The appearance of cortical bursts in early preterm neonates has been correlated with mental development and clinical evaluation? (Vecchierini et al. 2003; Iyer et al. 2015; Suppiej et al. 2015). During the maturation process, the dynamics of preterm brain networks can be viewed in terms of two processes that occur in parallel. One process is essentially progressive, characterized by a progressive decrease in discontinuity and amplitude and a gradual increase in dominant frequencies. The other process is characterized by the appearance of successive transient generators, observed during neural development of the last semester of pregnancy. These generators, angular frontal activities (24–30 wGA), theta temporal activities in coalescence with slow waves (TTA-SW) (24–32 wGA), delta brushes (28–36 wGA), frontal transient activity (34–42 wGA), with fairly specific spatial representation, can be considered to be functional neurobiomarkers of brain maturation (Pallas 2001; Tolonen et al. 2007). The absence or delayed appearance of these functional neurobiomarkers during the neurodevelopmental process is predictive of a poor functional prognosis (Vecchierini et al. 2003; Wallois 2010; Suppiej et al. 2015).

TTA-SW within the subplate constitutes a developmental neurobiomarker observed on the scalp EEG between 24 and 32 wGA. It is endogenously driven and located bilaterally in the temporal lobes beneath the posterior part of the Superior Temporal Sulci (STS) (Routier et al. 2017). Temporal theta activity likely plays a central role in the development of auditory and language processing abilities (Ayoub and Kostovic 2009; Routier et al. 2017). In parallel, as early as 28 wGA, the premature brain is already able to discriminate phonemes and voices in specific areas using neuronal strategies such as habituation and mismatch, which demonstrate a sophisticated organization of perisylvian areas at the very onset of cortical circuitry 3 months before term. These findings emphasize the influence of innate factors on regions involved in linguistic processing and social communication in humans (Mahmoudzadeh et al. 2013). Another characteristic indicator of the dynamic brain maturation process in premature infants is inter-hemispheric synchronization, which evolves from synchronization to non-synchronization and back to synchronization during neurodevelopment (Wallois 2010) in parallel with the development of tangential and interhemispheric connectivity.

Analysis of resting state functional connectivity (RSFC) in neonates by fMRI (Fransson et al. 2011; Omidvarnia et al. 2014) suggests that cortical hubs and their associated cortical networks are confined to the primary sensory and motor brain regions. Analysis with higher temporal resolution than fMRI is nevertheless mandatory in view of the specific dynamics of cortical activity in preterm. Bursts of activity in neonates showed strong spatial correlations, suggesting that the early developing human brain exhibits intermittent long-range spatial connections that likely provide endogenous guidance for early activity-dependent development of brain networks. Together with these bursts of activity, TTA-SW is considered to be one of the earliest functional neurobiomarkers that might play a determinant role in the wiring and functional shaping of the future neuronal network involved in language and communication processing. (Wallois 2010; Routier et al. 2017).

The aim of this study was to investigate the spatial organization of the influence of TTA-SW on the functional connectivity pattern of the early preterm brain during quite sleep. Fewer artefacts are observed during quite sleep due to fewer movements of neonates. For this purpose, High-Density EEG (HD-EEG) data of preterm infants were recorded to analyze the functional brain network in the premature brain (29–32 wGA). These analyses were designed to investigate two important questions: firstly, does TTA-SW influence cortical long-range connectivity in preterm infants? Secondly, what are the effects of TTA-SW on the spatial topology of local and whole brain connectivity?

Materials and Methods

Subjects

This retrospective study was based on HD-EEG (64 electrodes) analysis of 14 healthy preterm infants recorded for clinical follow-up between the ages of 29- and 32 wGA (mean GA at the time of recording: 31.26 ± 0.18 weeks, see Table 1) between December 2014 and June 2015. EEG data were recorded in the incubator in the Amiens University Hospital neonatal intensive care unit. All infants had appropriate birth weight, size and head circumference for their term age, and an APGAR (Appearance Pulse Grimace Activity Respiration) score higher than 6 at 5 min. Selected subjects also had normal auditory and very good clinical neurological assessments. Notably, neurological examination at the time of the recordings had to correspond to corrected GA, with no history of abnormal movements. Brain imaging, particularly transfontanellar ultrasound and standard EEG were normal. Exclusion criteria were preterm infants with neurological lesions such as intraventricular hemorrhage or any parenchymal malformation.

Table 1 Clinical data of the neonates

Gestational age at birth (weeks)	28 ± 1.91
Birth weight (g)	976 ± 266
Mean age at the time of EEG (weeks)	29 ± 1.76
Head circumference at the time of HD EEG (cm)	26 ± 2.19

The recording procedure was the same as that previously described (Routier et al. 2017). Over many years, we have developed painless caps to support a high-density array of sensors allowing HD-EEG recordings with 64 electrodes in preterm infants (Medelopt®). HD-EEG data were recorded at the bedside using Ag/AgCl surface electrodes and a nasion reference at a sampling rate of 1024 Hz, amplified by ANT® (Enschede, The Netherlands) or Compumedics® (Australia) and DC-75 Hz filtered. Electrode impedance was kept below 5 kΩ. Because of the rapid brain growth at this age, two caps were used to cover the normal range of head circumference (25 to 33 cm) during this period. EEG electrodes were placed on the classical 10–10 montage adapted to age in all infants (Acharya et al. 2016). We avoided using a binaural virtual electrode, which would have been located near the regions of interest and which could have been potentially contaminated by passive high-amplitude TTA-SW. Similarly, a virtual reference electrode consisting of the average of the active electrodes would have reintroduced TTA-SW in other electrodes, particularly because of the low-amplitude signal encountered during discontinuities in the contralateral hemisphere. The positions of the electrodes were digitized in the lab to fit the small head of neonates.

Selection of Theta Temporal Activities in Coalescence with Slow Waves (TTA-SW) (Figure 1)

To identify TTA-SW, HD-EEG data were analyzed by ASA (ANT® Software). Data were bandpass filtered (0.5–40 Hz) and down-sampled to 256 Hz, as this bandwidth eliminates infra-slow activities (Vanhatalo et al. 2004) and any DC current shift. TTA-SWs were selected on the basis of descriptions of the neonate's EEG features (Lamblin et al. 1999). To be eligible, TTA-SW had to be present over temporal electrodes. TTA-SWs were excluded when a concomitant artefact was present. TTA-SWs were selected manually using a marker positioned on the positive peak of the highest amplitude theta activity under the electrode providing the highest signal-to-noise ratio. TTA-SWs were selected under blinded conditions by two experienced electrophysiologists (FW and LR) and only TTA-SW identified by both electrophysiologists were finally selected. All the fourteen preterm infants had unilateral left TTA-SW and 11 of these preterm infants had unilateral right TTA-SW. Twenty-five 8-s segments centred on the peak of TTA-SW were selected for each subject.

EEG Data Preprocessing

In order to substantially improve spatial resolution by minimizing the volume conduction effect, EEG segments were re-referenced using a Laplacian montage (current source density, CSD) (Perrin et al. 1989; Srinivasan et al. 2007) using the following settings: spline flexibility, $S = 4$ and smoothing parameter, $\gamma = 1 \times 10^{-5}$. We repeated the experiment with different spline flexibility ranging from $S = 4$ to 10 and did not observe any difference in EEG power. The effect of the spline flexibility was tested on the functional connectivity (Figure S1) but no significant differences were observed between the FC strength with spline flexibilities of 4,6,8 and 10. Missing or noisy channels were interpolated using spherical interpolation to avoid loss of information at border locations (Kayser and Tenke 2015). The number (maximum 3) of interpolated channels was so low as to be significantly confounding for our results. After removal of the missing or noisy channels, 60 electrodes were considered across all neonates for further analysis by an EEGLAB and fieldtrip custom script in the MATLAB environment.

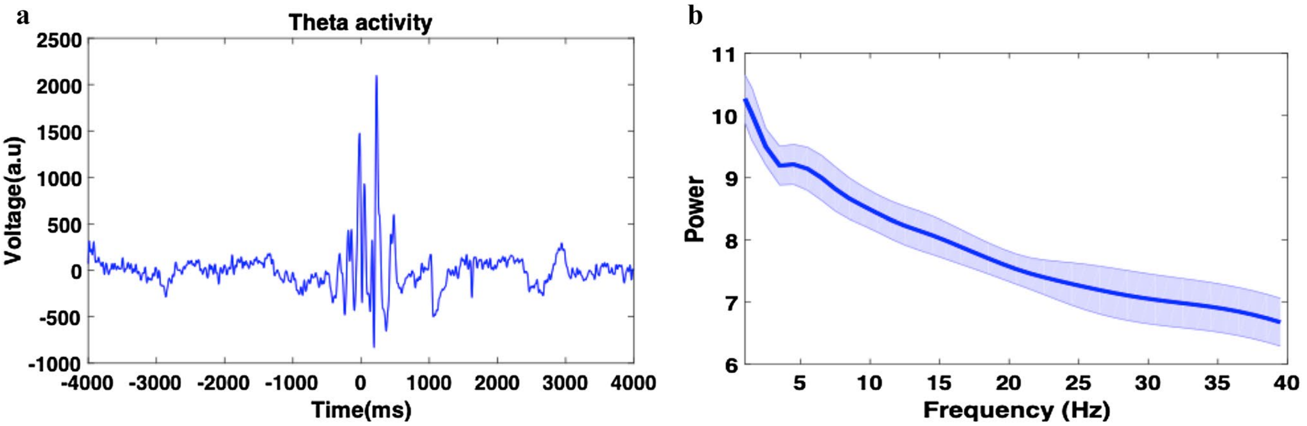

Fig. 1 Theta temporal activity in coalescence with slow waves: **a** TTA-SW of one subject at one of the temporal electrodes (T7) shows higher amplitude of the theta waves in coalescence with the slow delta activity. Theta activity occurred within 200 to 500 ms. **b** The power spectrum (in dB), between 200 and 400 ms, of all subjects shows increased power at theta bands, corresponding to theta activity

Functional Connectivity

Unlike adult EEG signals, δ and θ signals are the predominant frequency bands observed in preterm neonate EEG (André et al. 2010; Wallois 2010). However, we extended this study to the 0.5 to 20 Hz frequency range. The frequency range was subdivided into 5 frequency bands: delta (0.5–4.0 Hz), theta (4.5–8.0 Hz), alpha (8.5–12.0 Hz), beta1 (12.5–16.0 Hz) and beta2 (16.5–20.0 Hz), using a bandpass linear-phase FIR (finite impulse response) filter with zero-phase forward and reverse digital filtering.

The complex analytical signals were obtained by Hilbert transformation of the filtered signals. The Hilbert transformed signals consisted of the instantaneous amplitude and phase of the signals. The complex analytical signals (x (t, f)) were first computed by:

$$\check{x}(t,f) = x(t,f) + ix_H(t,f)$$

where x_H (t, f) is the Hilbert transform of the input signals x (t).

Connectivity measures based on specific spectral components provide qualitatively new insight into brain activity, but scalp EEG recordings are limited by their poor spatial resolution making distant sensors sensitive to the same neuronal sources. However, several FC measures have been developed, especially for adult EEG/MEG, to limit the effect of volume conductions. In the present study, FC between EEG channels was computed by the power envelope correlation of orthogonalized signals, which has been shown to discount the spurious correlation pattern caused by the limited spatial resolution of electrophysiological signals (Hipp et al. 2012). This approach has already been used to study functional connectivity in neonates (Omidvarnia et al. 2014). This technique uses the orthogonal projection of one signal on another to reduce the common instantaneous amplitude components, and is implemented as follows:

$$X_{1\perp X_2}(t,f) = imag\left(X_1(t,f)\frac{X_2(t,f)^*}{\left|X_2(t,f)\right|} \right)$$

The above equation computes the orthogonalized time-series signal from channel X_1 to channel X_2, where X is the complex analytical signal obtained by the Hilbert transform (Hipp et al. 2012). X^* is the complex conjugate and *imag* indicates the imaginary conjugate. Power envelope correlations were computed for both directions (from X1 to X2 and from X2 to X1) of the orthogonalized time-series. The values of correlation were then averaged over all epochs for subsequent analysis. This process was repeated between all pairs of channels and all frequency bands for each subject. The end-result provided an adjacency functional connectivity (non-directional connectivity) matrix for each computation of paired combinations of EEG channels.

Brain Network Analysis

Neonatal cortical network activities, as revealed by EEG, are different from those of mature adults due to the emergence of specific features during the course of development (Vecchierini et al. 2003, 2007). However, in this study, we specifically analysed FC of one of the earliest biomarkers of the premature brain: the theta temporal activity in coalescence with Slow Wave (TTA-SW). The functional strength of the functional network was computed in order to evaluate the transient changes in the dynamics of brain activity during TTA-SW. Network analysis of brain function started with definition of the interacting units (nodes) and quantitation of the interactions (edges). This study was conducted according to standard practices in the field of neuroimaging. We defined nodes as electrode positions and edges as FC strengths between the corresponding nodes (Rubinov and Sporns 2010). The strength of FC at electrode location was therefore computed to measure the dynamics and spatial characteristics of the weighted FC matrix. The strength (or degree) is a characteristic measure of functional interactions between brain regions (in this case electrodes). A region or electrode with a high degree or strength has a large number of connections with the other regions or electrode. The strength of FC at electrode location (Rubinov and Sporns 2010) is computed as follows:

$$K_i = \sum_{J\in N} a_{ij}$$

where a_{ij} is the connection strength between electrodes i and j, and N is the total number of links between all electrodes in the network. K_i is the strength of FC at electrode location.

In summary, the FC between paired electrodes (Fig. 2a) was computed by the power envelope correlation (Hipp et al. 2012) of orthogonalized signals, which has been shown to have a minimal effect and a spurious volume conduction effect. The end-result produced a functional connectivity matrix (Fig. 2b), which consists of the connectivity strength between electrodes for each frequency band. To investigate brain network organization, functional connectivity was characterized by the strength of FC at electrode location (Fig. 2c).

Statistical Analysis

The significance of each pair of correlations or each FC between pairs of EEG channels was tested by performing a fully nonparametric regional permutation test with 1000 randomizations (Maris 2012). Phase randomization was performed to obtain a null distribution of the noise

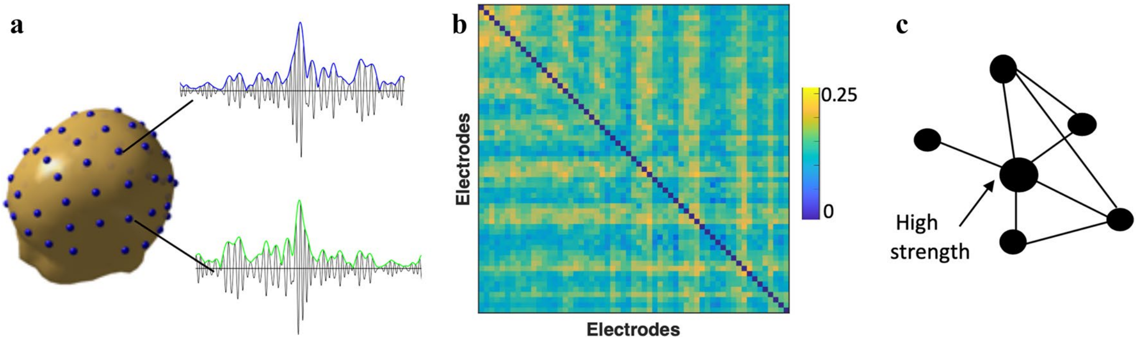

Fig. 2 Brain network construction: **a** Functional connectivity between paired EEG channels was computed by the power envelope correlation of the EEG signals, which produced a functional connectivity matrix **b** between the paired EEG electrodes. **c** The functional connectivity matrix was characterized by the strength of the brain network. A node at the centre has the higher strength because of its connection to all other nodes in the network

correlation values and to compare with the real correlation values. Only real correlation value above the noise correlation values were considered significant. This corresponds to a common practice for time series signal processing for testing significancy of functional correlation. Each time series signal was phase-randomized to reduce the effect of phase and create surrogate data with the same distribution of original data. The power envelope correlation, as described above, was computed for each set of surrogate data. To correct for multiple comparisons, the maximum value of correlation in a given permutation procedure was selected and the threshold for a pair correlation was defined as q*100th percentile of the null distribution of maximum values. The threshold was set at $q = 0.01$ and only significant correlations between pairs of each channel above the threshold were included in the functional connectivity matrix.

Nonparametric permutation testing was used for all network metrics with correction for multiple comparisons. Network metric and functional connectivity matrices were normalized with a mean of 0 and a variance of 1 for each preterm infant to allow comparison of networks between individuals. For all group-level statistics or comparisons between groups, a total of 1000 permutations were used to determine the significance level for each test including functional connectivity matrices. One-way ANOVA was applied to the study to estimate the difference between the group. All computations and statistical analyses were performed in Matlab and open source toolboxes: EEGLAB (for 3D topological plots, http://sccn.ucsd.edu/eeglab/).

Results

Theta Temporal activities in coalescence with slow waves (TTA-SW) occur around 26 to 32 weeks of gestational age (André et al., 2010) in one or both temporal regions. TTA-SW consists of high-amplitude theta activity in coalescence with slow waves (Selton et al. 2000; Vanhatalo and Kaila 2006; André et al. 2010; Wallois 2010) (Fig. 1). However, in this study, we investigated the influence of TTA-SW on the functional brain network of 14 preterm neonates. 14 presented left TTA-SW and 11 of them presented also right TTA-SW.

Influence of TTA-SW on Whole Brain Functional Connectivity

To investigate the influence of TTA-SW on the whole brain FC of the premature brain, FC was computed in 2-s epochs in the 8-s segments selected around the TTA-SW peak ($t = 0$): 2 s centred around the peak of the TTA-SW ($-1; +1$ s) (during TTA-SW; DT), 2 s before (BF) TTA-SW ($-3; -1$ s), and 2 s after TTA-SW ($+1; +3$ s) (AF). Paired *t* test was used to compare FC for BF, DT and AF segments, separately for left and right TTA-SW. Functional connectivity increased significantly during right and left TTA-SW (DT) in comparison with BF in the theta band (Fig. 3). The presence of TTA-SW in the left temporal regions (Fig. 3a) increased FC between the left temporal and left frontal and the left parietal areas ($p < 0.0001$). Significant FC ($p < 0.0005$) was also observed in the presence of right TTA-SW (Fig. 3b) between the left frontal and left parietal areas, especially in the theta band. The presence of left TTA-SW (DT) increased FC compared to AF in the theta band ($p < 0.0006$) and, to a lesser extent, in the alpha band ($p < 0.0002$) between left temporal and parietal areas (Supplementary Figure 1). Comparison between AF and BF (but not DT) for TTA-SW showed significantly weaker FC only for the left hemisphere ($p < 0.018$) (Figure S2) but restricted to the left frontal and left parietal areas in the theta band.

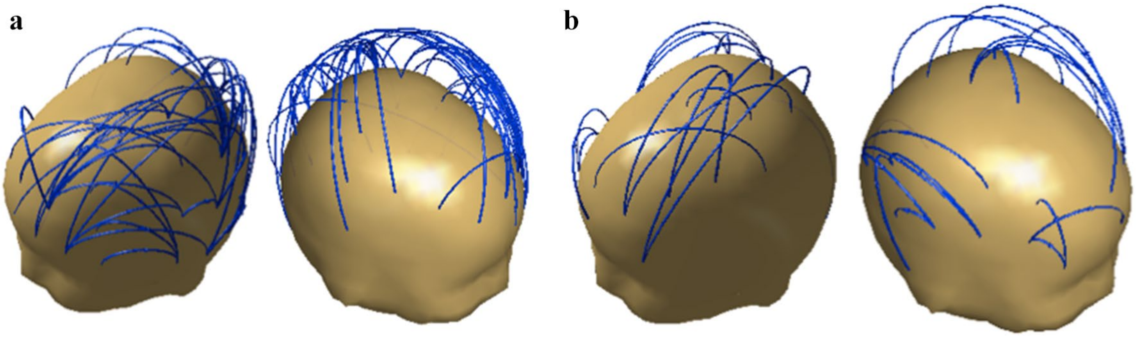

Fig. 3 Functional connectivity pattern during TTA-SW. Comparison of functional connectivity during TTA-SW (DT) and before TTA-SW (BF) in the theta band (4–8 Hz) revealed **a** significant functional connectivity ($p = 0.0001$) in the left temporal region of left TTA-SW subjects' group and connectivity from the left temporal region to the frontal and posterior regions. **b** Right TTA-SW subjects also presented significant FC when comparing BF vs DT ($p = 0.0005$) in the right temporal region and from the central to the frontal regions

Premature Brain Network Influenced by TTA-SW

In the previous section, we showed that TTA-SW influenced the FC between temporal, frontal and parietal areas. In this section, we investigate how the brain network is influenced by the presence of TTA-SW.

Functional strength globally increased in the theta and alpha bands in the presence of left (Fig. 4a) and right TTA-SW (Fig. 4b). T-test statistical analysis showed that functional strength increased significantly during left TTA-SW (Fig. 4a) in all frequency bands, except for the delta band, but was significant in the theta band for right TTA-SW (Fig. 4b). Functional strength was higher during TTA-SW (DT) especially in theta band and was markedly different from before (BF) or after (AF) TTA-SW (Fig. 4a). Analysis of the spatial distribution of functional strength showed significant functional strength in the temporal area during TTA-SW (DT) compared to before TTA-SW (BF) (Fig. 4c–f). Comparison of DT to BF in the theta band for left TTA-SW (Fig. 4c) and right TTA-SW (Fig. 4d) showed higher strength in the left and right temporal areas, respectively. Figure 4e, f show functional strength (DT > BF) in the alpha band for left and right TTA-SW, respectively. Comparison between DT and AT revealed significantly weaker functional strength with the presence of left TTA-SW in the same temporal areas (Figure S3).

Transient Changes in the Dynamics of the Brain Network During TTA-SW

TTA-SW is a specific and brief (1 to 2 s) feature. The dynamics of TTA-SW are not clearly understood, but likely consist of a high-amplitude theta wave in coalescence with a delta wave (Routier et al. 2017). We therefore computed FC with 2-s sliding windows and 95% overlap. Functional strength was computed from dynamic FC for each EEG channel.

Global strength, average functional strength over all EEG channels, was analysed (Fig. 5. Global strength decreased in the delta band at maximum theta activity, as shown in Fig. 5a, b for left and right TTA-SW, respectively. In the theta band for left and right TTA-SW (Fig. 5c, d, respectively), global strength presented an M-shape, and was higher at the onset of TTA-SW and decreased during TTA-SW to rise again to higher values before returning to the baseline level before the TTA-SW. These M-shapes were also observed in the alpha and beta bands (Figure S4).

Local Dynamic Organization of the Brain Network During TTA-SW

In order to investigate the local dynamic organization of the brain network during TTA-SW, the dynamics of the spatial distribution of the functional strength were extracted from 5 specific annotated points selected from the global strength curves described in the previous section. Point A (Fig. 6) corresponds to 2 s before TTA-SW, while points B and D correspond to the 2 peaks of maximum global strength during TTA-SW and point C corresponds to the lowest global strength during TTA-SW between two peaks (B and D). Figure 6b shows the comparison of the significance of spatial distribution of local strength between points B, C and D and point A. For left and right TTA-SW, points B, C and D were considered with respect to point A (control). Functional strengths were significantly (t-test) higher over the bilateral temporal areas (situated more rostrally during right TTA-SW) and over the left frontal area for both right and left TTA-SW. Comparison of point B and point A during left TTA-SW revealed a spurious increase in functional strength over the contralateral right temporal area. Functional strength also briefly increased over bilateral central areas adjacent to the midline. The spatial extent of the significant increase in functional strength at point C appeared to be more restricted to the source of TTA-SW and frontal

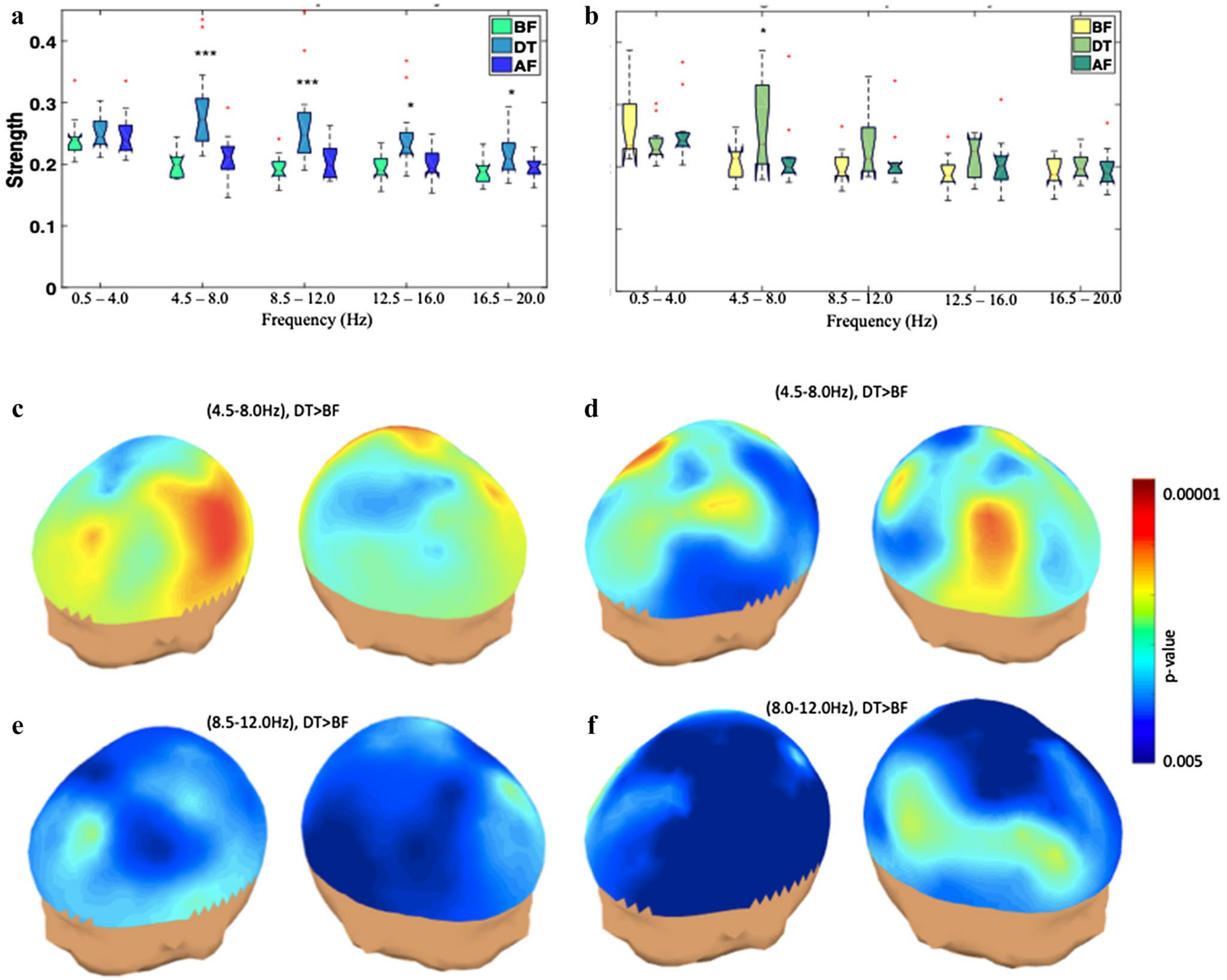

Fig. 4 Functional strength: **a** and **b** show the global strength for both left and right TTA-SW, respectively, during (DT), before (BF) and after (AF) TTA-SW. Comparison of DT to BF in the theta band for left TTA-SW **c** and right TTA-SW **d** shows significant strength in the temporal areas (source of TTA-SW) and ipsilateral frontal regions. Functional strength was less significant in the alpha band: **e** left TTA-SW and **f** right TTA-SW. (one-way ANOVA, $*p<0.05$, $**p<0.01$, $***p<0.0001$)

areas, but was more widespread at points D and B. In the delta band, higher functional strength was observed in both temporal areas and in the left central area adjacent to the midline (Figure S5).

Discussion

This is the first evaluation of FC and brain network organization in preterm neonates using 64-channel HD-EEG. The results of this study strongly suggest that the endogenous neurobiomarker of neural development in perisylvian areas has an influence on the functional organization of the preterm brain networks and is likely to participate in the prewiring of the perisylvian network involved in language and social interactions.

Impact of TTA-SW on Local and Global Early Brain Network Organization

We have shown that TTA-SW establishes regional connectivity between temporal, frontal and parietal areas regardless of whether the source of TTA-SW was located in the right or left hemisphere. TTA-SW is a spontaneous, endogenous non-sensory-driven generator located in the subplate (Routier et al. 2017) and is one of the earliest neurobiomarkers of brain development in preterms (Wallois 2010). A previous optical imaging study using fNIRS (Mahmoudzadeh et al. 2013) clearly demonstrated that, from the age of 28 wGA,

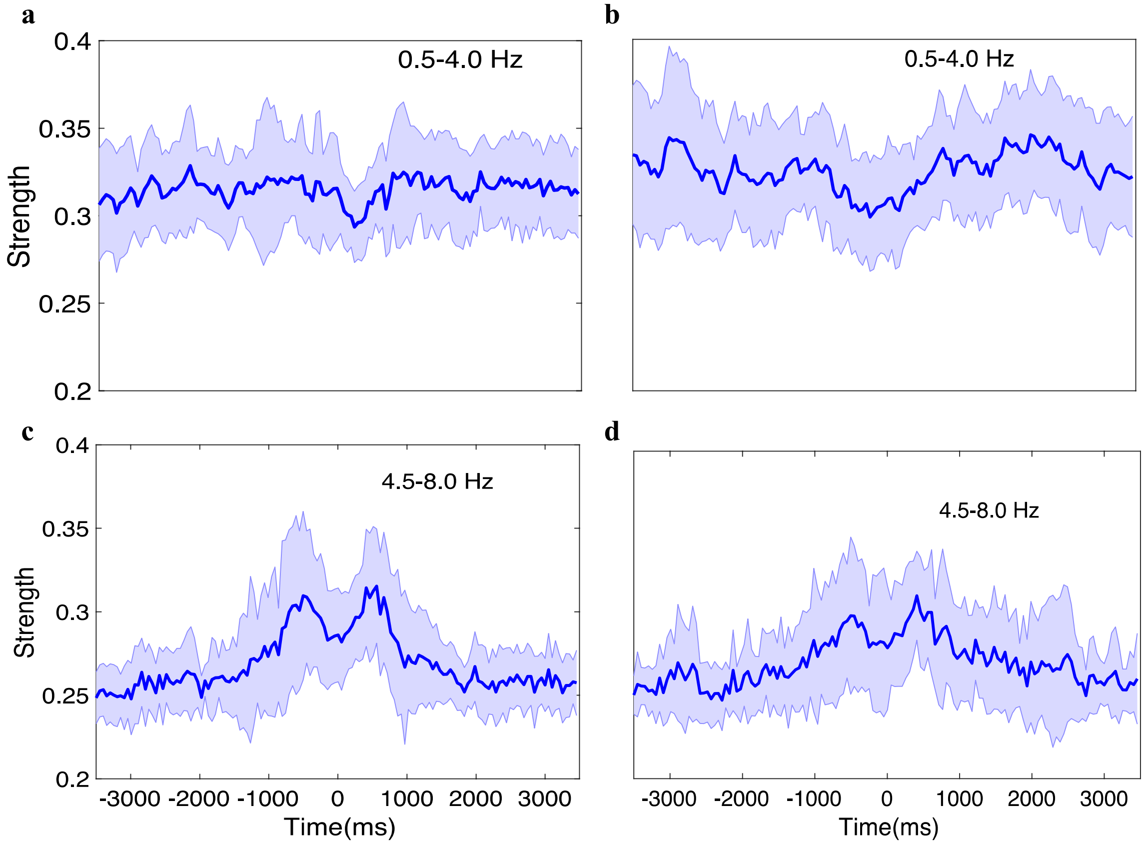

Fig. 5 Dynamic global strength. Global strength presented different dynamic features for the delta band (0.5–4.0 Hz) and the theta band (4.5–8.0 Hz). **a** and **b** show that the global strength decreased during theta activity in the delta band for left and right TTA-SW, respectively, while global strength presented an M-shape in the theta band **c**, **d** for left and right TTA-SW, respectively. The M shape in theta band reflects the dynamics of temporal theta activity during the brief TTA-SW event. The onset and disappearance of TTA-SW therefore had a global influence on brain network organization

perisylvian structures, such as the planum temporale, STS and inferior frontal gyri, are already involved in the processing of linguistic information. All of these findings suggest a strong genetic fingerprint for the development of these early capacities in specific areas that are subsequently activated in adults when exposed to the same stimuli. In the light of recent studies (Mahmoudzadeh et al. 2013; Leroy et al. 2015; Routier et al. 2017), we hypothesized that functional prewiring of the perisylvian area was already present before the connection of the cortical plate with auditory afferent information. The early wiring and the development of neuronal networks that participate in sensory integration constitute a key element of neuronal development and depend on the fine tuning between genetic factors and endogenous activities that provide guidance for early brain wiring and optimization of synaptic connections (Penn and Shatz 1999; O'Leary et al. 2007; Tritsch et al. 2010). Spontaneous endogenous activities, such as TTA-SW, constitute an omnipresent characteristic of the developing neuronal network and are considered to provide important depolarization input (Blankenship and Feller 2010). Even before sensory structures are able to perform functional activity, endogenous mechanisms induce bursts of spontaneous activities separated by long quiescent periods. This type of spontaneous activity in the developing auditory system is necessary for the survival, optimization and maintenance of brain tonotopic maps (Tritsch et al. 2010). Spontaneous activities independent of any sensory experiences precede the emergence of visual, auditory or somatosensory capacities, suggesting that neocortical neural networks are capable of generating spontaneous oscillatory patterns and that these patterns may represent a substrate for the formation of the first functional networks (see (Kilb et al. 2011) for review).

Because of the location of their source and their onset starting from 24 wGA, TTA-SW are good candidates for this type of oscillatory pattern. Interestingly, the results of the present study show that TTA-SW reinforce FC between the temporal, frontal and parietal areas, which supports the possible role of TTA-SW in prewiring or functional optimization of the perisylvian areas. TTA-SW sources are located in the subplate (Routier et al. 2017), which is involved in the shaping or optimized definition

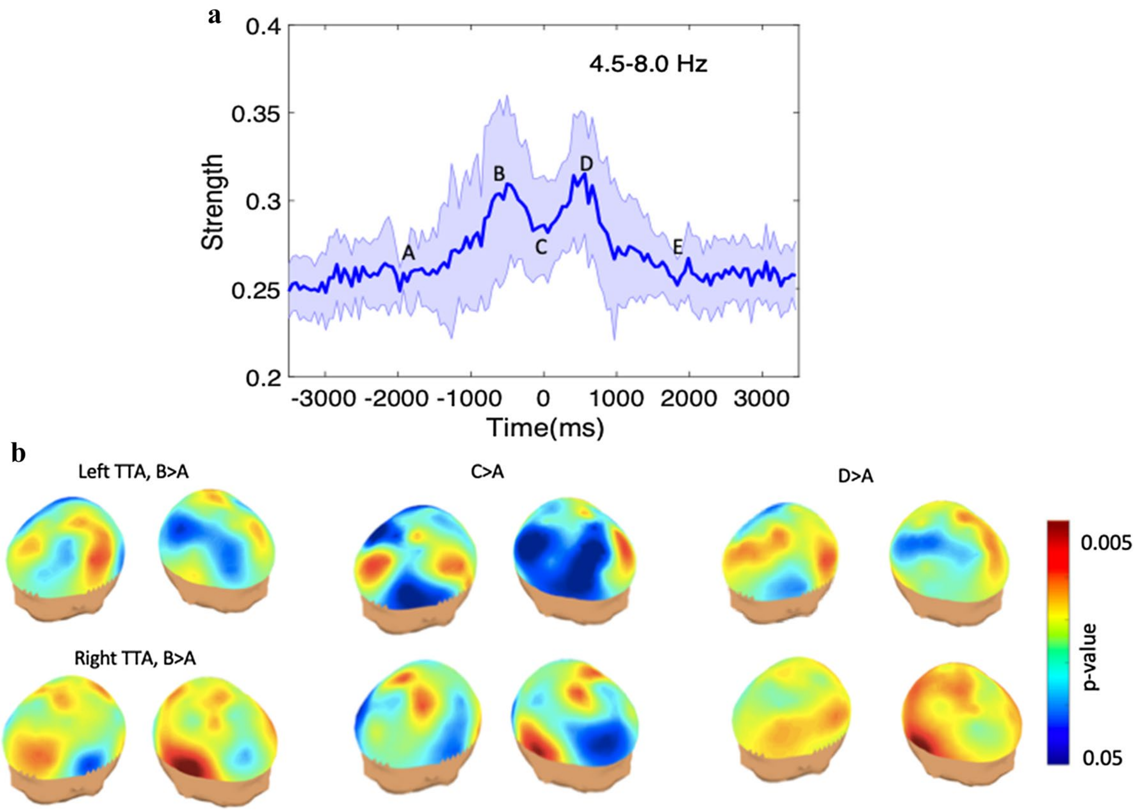

Fig. 6 TTA-SW dynamic features in the theta band. **a** Five points were identified. Points B and D correspond to maximum global strength and point C is situated between points B and D. These points (B, C and D) were compared to points A before the onset of TTA-SW. **b** Comparison of point B and point A shows increased functional strength (B > A) in bilateral temporal regions at the onset of TTA-SW, including frontal and posterior regions. At point C compared to A, functional strength was significantly increased only in the temporal region (source of TTA-SW) and ipsilateral frontal region for both left and right TTA-SW. The dynamic TTA-SW features changed at point D (compared to A), resulting in significantly increased functional strength over almost all brain areas

of the future functionality of the cortical plate. The site of TTA-SW is therefore appropriate to this function.

Schematically, TTA-SW might participate in the transmission of specific information traveling along the arcuate fasciculus that connects the superior temporal sulcus (STS) to the inferior frontal gyrus. TTA-SW appears to convey functional messages or neural signals to other neuronal targets (optimization and refinement of cortical connections). TTA-SW may also participate in the development of the well time-locked sequential interactions between these specific areas along the arcuate fasciculus (Mahmoudzadeh et al. 2013). TTA-SW disappear progressively after 32 wGA, suggesting that the enhanced functionality described in this study before 32 wGA progressively disappeared in parallel with disappearance of the subplate, in contrast with the thalamocortical connections that convey specific auditory inputs to the auditory cortex, which develops considerably after 32 wGA.

Asymmetry in the Functional Connectivity Related to TTA-SW

The enhanced FC pattern differs between the left and right TTA-SW. The left TTA-SW shows significant FC between temporal, frontal and parietal areas in the left hemisphere only, while significant FC with the right TTA-SW is restricted to the right temporal region. This hemispheric specificity may suggest differences in the functional wiring of the left and right TTA-SW. Dynamic of the hemodynamic response to phonemes and vocal stimulation clearly reveals a leftward followed by a rightward perisylvian asymmetry during auditory processing (Mahmoudzadeh et al. 2013), implying that, from the age of 28 wGA, a strong alternating interaction already exists between the two hemispheres. Various structural factors may also contribute to the differences in the connectivity patterns of left TTA-SW and right TTA-SW. Notably, the arcuate fasciculus that links the posterior superior temporal sulcus (STS) to the inferior frontal gyrus is already well developed in 28 wGA preterm neonates, but with a leftward asymmetry (Leroy et al. 2015). Such advanced maturation of the left arcuate fasciculus could at least partly explain the significant FC between the left inferior frontal and left parietal areas both related to left TTA-SW. The bilateral effect of TTA-SW might be more visible on the left hemisphere because the left arcuate fasciculus matures more rapidly than the right arcuate fasciculus (Glasel et al. 2011; Leroy et al. 2015). Nevertheless, this assumption requires further evaluation. In summary, our results provide arguments for the involvement of these TTA-SW in the prewiring of perisylvian regions by providing a repetitive endogenous input, which, together with regional patterning of gene expression (Johnson 2001), might participate in the early functional tuning of this network.

Functional Strength Distribution During TTA-SW

Functional strength estimates the centrality of the brain regions and the brain regions with higher functional strength interact and facilitate functional integration with other regions (Tononi et al. 1994). Higher significant functional strength in the frontal and parietal areas during TTA-SW suggests that these regions provide a foundation for coherent neuronal activation across distal cortical regions (Kostovic and Judas 2010; Judaš et al. 2013). It also suggests that these bilateral regions play a key role in brain network functional integration early in development. Significant functional strength is situated more anteriorly in the right temporal area than in the left temporal area, in line with the Yakovlean torque that pushes the right hemisphere above and in front of the left hemisphere and displaces the right Sylvian fissure and right superior temporal sulcus more dorsally and more anteriorly than their left counterparts (Leroy et al. 2015). As observed in preterm neonates, the frontal and parietal area have been considered to be structural and functional hubs in neonates (Ball et al. 2014; van den Heuvel et al. 2015) and in adults (van den Heuvel and Sporns 2013). These results are consistent with the general idea that brain networks evolve from a dense local architecture dominated by frontal, temporal and parietal areas in immature neuronal circuits towards a more diffuse topology in adults (Fair et al. 2009; Dosenbach et al. 2010).

Global Strength Indicates the Coalescence Between Theta and Delta Activity During TTA-SW

TTA-SW corresponds to the coalescence of at least 2 generators (delta and theta) that are coactivated with a fixed time-lag relationship (Routier et al. 2017). The dynamic relationship between these 2 coalescent generators is of interest, as they may participate in different functional targets. The M shape of the global strength in theta band during TTA-SW occurred at the same time in the delta band at minimum global strength. The rise of global strength in the theta band implies that their network connections are relatively denser than in other frequency bands.

The dynamics of the spatial distribution of the functional strength during TTA-SW show that the significant functional strength was restricted to the left posterior temporal and frontal areas or right temporal area especially during the left TTA-SW. This is consistent with the idea that TTA-SW activity participates in the refinement of perisylvian functional development (Penn and Shatz 1999).

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