Published in final edited form as:

J Neurosci Methods. 2016 September 01; 270: 76–84. doi:10.1016/j.jneumeth.2016.06.009.

Effect of Electrocardiogram Interference on Cortico-Cortical Connectivity Analysis and a Possible Solution

R. B. Govindan^a, Srinivas Kota^a, Tareq Al-Shargabi^a, An N Massaro^b, Taeun Chang^c, Adre du Plessis^a

^aDivision of Fetal and Transitional Medicine, Fetal Medicine Institute, Children's National Health System, 111 Michigan Ave, NW, Washington, DC 20010, USA

^bDivision of Neonatology, Children's National - 111 Michigan Ave, NW, Washington, DC 20010, USA

^cDivision of Neurology, Children's National - 111 Michigan Ave, NW, Washington, DC 20010, USA

Abstract

Background—Electroencephalogram (EEG) signals are often contaminated by the electrocardiogram (ECG) interference, which affects quantitative characterization of EEG.

New Method—We propose null-coherence, a frequency-based approach, to attenuate the ECG interference in EEG using simultaneously recorded ECG as a reference signal. After validating the proposed approach using numerically simulated data, we apply this approach to EEG recorded from six newborns receiving therapeutic hypothermia for neonatal encephalopathy. We compare our approach with an independent component analysis (ICA), a previously proposed approach to attenuate ECG artifacts in the EEG signal. The power spectrum and the cortico-cortical connectivity of the ECG attenuated EEG was compared against the power spectrum and the cortico-cortical connectivity of the raw EEG.

Results—The null-coherence approach attenuated the ECG contamination without leaving any residual of the ECG in the EEG.

Comparison with Existing Method—We show that the null-coherence approach performs better than ICA in attenuating the ECG contamination without enhancing cortico-cortical connectivity.

Conclusion—Our analysis suggests that using ICA to remove ECG contamination from the EEG suffers from redistribution problems, whereas the null-coherence approach does not. We show that both the null-coherence and ICA approaches attenuate the ECG contamination. However, the EEG

Address for correspondence: Dr. R. B. Govindan, Staff Scientist III, Director of Advanced Physiological Signals Processing Lab, Division of Fetal and Transitional Medicine, Fetal Medicine Institute, Children's National Health System, 111 Michigan Ave, NW, Washington, DC 20010, rgovinda@childrensnational.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of Interest
None declared

obtained after ICA cleaning displayed higher cortico-cortical connectivity compared with that obtained using the null-coherence approach. This suggests that null-coherence is superior to ICA in attenuating the ECG interference in EEG for cortico-cortical connectivity analysis.

Keywords

coherence; transfer function; independent component analysis; electrocardiogram; electroencephalogram; cortico-cortical connectivity

1. Introduction

An electroencephalogram (EEG) allows for continuous bedside monitoring of electrocortical activity in critically ill infants with high temporal resolution. [1–11] Spectral and connectivity analyses are commonly used to characterize the EEG signal. EEG monitored in a critical care setting is highly vulnerable to artifacts from several non-physiological and physiological sources. Examples of non-physiological sources include power lines, interference from the ventilator, and movement artifacts. The presence of artifacts affects quantitative characterization of the EEG signals and analysis of cortico-cortical connectivity analysis as well. These artifacts can be attenuated by using appropriate digital filters and by setting upper and lower margins to the EEG. Examples of physiological sources include eye blinks, eye movements, and electrocardiograms (ECG). For single channel measurement, eye blinks and eye movement artifacts can be identified using a template matching approach, and discarded from further analysis. For multichannel EEG, the eye blink and eye movement artifacts can be removed using a blind source separation technique such as independent component analysis (ICA) or principal component analysis. For ECG artifacts, several different approaches have been proposed including ICA [12, 13], a template-based subtraction, [14, 15] and a hybrid version of ICA, which is a combination of a wavelet transform and ICA.[16] Techniques such as ICA and its hybrid version do not need a reference electrocardiogram (ECG) recorded simultaneously with EEG to attenuate the cardiac artifacts. However, the template-based cardiac artifact removal techniques require simultaneous measurement of ECG along with EEG. Simultaneous acquisition of ECG along with EEG signals has been a standard practice in sleep studies and in other routine clinical monitoring.[17, 18] The ECG recorded in those studies can be employed to attenuate the ECG artifacts in EEG.

In ICA, the EEG signals are decomposed into independent components and the components containing ECG cycles are identified. In most applications, this step is done in an automatic manner using the characteristics of ECG.[19] The clean EEG is obtained by transforming the ICA components back to the sensor domain after nulling the components containing the ECG cycles. In some cases, not all components containing ECG cycles are reliably identified, which leaves residual ECG signals in the ‘cleaned’ EEG. In other instances, components that do not contain ECG cycles are identified by the automatic schemes, leading to attenuation of the EEG signal. While the template subtraction approach would yield reliable results if the data were artifact free, the data acquired from sick infants in a critical care setting may be highly contaminated with artifacts.[20] Hence, this method is not robust when collecting data from sick infants in the critical care unit.

A frequency-dependent subtraction approach has been proposed to attenuate the interfering maternal and fetal cardiac signals for fetal magnetoencephalogram analysis.[21] In [21], using a heuristic approach, a small group of sensors containing predominantly maternal and fetal cardiac signals were selected as references. To attenuate the interfering signals, the Fourier transform of the signal from each sensor was negated from the weighted Fourier transforms of the reference signals using transfer functions as weights. One limitation of this approach is that sensors chosen as references cannot be used for further analysis as they contain zero values at the end of this operation. To overcome this limitation, we propose a modification to the frequency dependent subtraction approach, which uses only one reference signal to attenuate the interference signal. We validate the proposed approach using numerically simulated data and demonstrate the application of the approach using EEG collected from six newborns with hypoxic-ischemic encephalopathy (HIE) undergoing continuous EEG monitoring. [22]

We compared the performance of our null-coherence approach against that of ICA, a commonly used approach to attenuate artifacts in spatio-temporal signals. To assess the performance, we compared the power spectra and cortico-cortical connectivity measures of the clean EEG obtained from null-coherence and ICA. We demonstrated that EEG cleaned using ICA suffers from signal redistribution, which is a common problem with a spatio-temporal analysis approach.[23] In contrast, the EEG cleaned using the null-coherence approach does not suffer from this problem.

2. Materials and Methods

2.1 Clinical:

We studied six encephalopathic newborns undergoing therapeutic hypothermia in the neonatal intensive care unit according to the National Institute of Child Health and Development Research Network protocol.[24] Continuous (11-channel) EEG monitoring (NicoletOne™, Viasys Healthcare, San Diego, CA, USA), is routinely initiated as soon as possible after admission (median 17.2 [8.13 24] hours) and continued through the completion of treatment (minimum 72 hours). The EEG was sampled at 256 Hz and high-pass filtered online at 0.1 Hz. An anti-aliasing low-pass filter at 70 Hz was also used online. In offline analysis, the baseline drift was attenuated using a high-pass filter of 0.5 Hz. To attenuate the power line artifact, a notch filter at 60 (59–61) Hz was used. All the filtering process was done using a fourth order Butterworth filter with no phase distortion. Infants were part of an ongoing prospective observational study evaluating physiological biomarkers of brain injury in newborns with HIE. The Children's National Institutional Review Board approved the study and an informed consent was obtained from the parent of the participant for data collection.

2.2 Null-coherence:

In the null-coherence approach, the reference and the source signals are modeled as input-output impulse response, respectively. To attenuate the interfering ECG signal, the reference signal (ECG) and the source signal (EEG) were partitioned into 1-minute windows, which we will call processing windows. To estimate the spectral quantities needed to attenuate the

interference signal, the data in the 1-minute windows were divided into 3-second epochs. [25] For the data in each epoch, the mean value was subtracted and divided by the standard deviation and the Fourier transform was calculated. In the j -th 3-second, we denote the Fourier transforms of ECG and EEG as $F_{ECG}^j(\omega)$ and F_{EEG}^j , with ω being the frequency in Hz, respectively. The Fourier transforms of ECG in each 3-second window was multiplied by the median of the standard deviation of the ECG over all 3-second windows. Similarly, the Fourier transform of EEG in each 3-second window was multiplied by the median of the standard deviation of the EEG over all 3-second windows. In each 3-second epoch, the periodograms of ECG and EEG were defined as the square of the magnitude of the respective Fourier transforms. Similarly, the cross-spectrum between ECG and EEG was defined as the product of the $F_{ECG}^j(\omega)$ and the complex conjugate of $F_{EEG}^j(\omega)$. To this end, the estimates of the power spectrum of the ECG ($S_{ECG}(\omega)$) and EEG ($S_{EEG}(\omega)$) were defined as the average of the respective periodograms over all 3-second epochs. Similarly, the estimate of the cross-spectrum ($S_{ECG,EEG}(\omega)$) was defined as the average of the cross-spectra over all 3-second epochs. To this end, coherence between ECG and EEG was defined as the ratio of the square of the magnitude of the cross-spectrum to the product of the power spectra of ECG and EEG. Mathematically, coherence is defined as follows:

$$Coh_{ECG, EEG}(\omega) = |S_{ECG, EEG}(\omega)|^2 / S_{ECG}(\omega) \cdot S_{EEG}(\omega), \quad (1)$$

where $|\cdot|$ denotes the magnitude operation. Coherence takes on a value of one in cases of perfect synchrony between two signals and a value of zero in cases of asynchrony between them. The confidence limit of coherence at the $100\alpha\%$ level is given by $1 - (1 - \alpha)^{1/M} - 1$, with M being the number of epochs involved in the estimation of the spectral quantities.[25] In our calculation, was set to 0.999. If the coherence in a chosen frequency band was greater than the confidence limit, it was considered statistically significant. The impulse-response transfer function was defined as follows:

$$H_{ECG, EEG}(\omega) = S_{ECG, EEG}(\omega) / S_{ECG}(\omega). \quad (2)$$

Using the transfer function, the ECG in j -th 3-second epoch was attenuated as follows:

$$G_{EEG}^j(\omega) = F_{EEG}^j(\omega) - H_{ECG, EEG}^\dagger(\omega) \cdot F_{ECG}^j(\omega), \quad (3)$$

where $\dagger$ indicates the complex conjugate operator. $G_{EEG}^j(\omega)$ is the Fourier transform of ECG subtracted EEG in the j -th 3-second epoch, which was then inverse Fourier transformed to obtain clean EEG in time domain. This procedure was repeated for every 3-second epoch in the processing window. The various steps involved in the cleaning of ECG using the null-coherence approach are demonstrated in a flowchart shown in Figure 1.

2.3 Independent Component Analysis

In ICA, the given multidimensional EEG signals (denoted by $X(t)$) are decomposed into independent components using the following model:

$$X(t) = A \cdot S(t), \quad (4)$$

where A is called mixing matrix and $S(t)$ is the matrix containing the independent components. There are several numerical approaches to calculate A and $S(t)$ of which the most commonly used is the Adaptive Mixture ICA implemented in EEGLAB.[26] We studied coherence between each ICA component and the ECG. The components that showed significant coherence were identified as the ones that contained ECG cycles. In our datasets, two to three ICA components had ECG cycles and in $S(t)$ these components were set to zero. We denote the modified $S(t)$ as $S'(t)$. The clean EEG was obtained by multiplying A with $S'(t)$.

In the foregoing discussion we will denote raw EEG as EEG_{Raw} and EEG obtained using null-coherence and ICA approaches as EEG_{NC} and EEG_{ICA}, respectively.

2.4 Performance Assessment using Cortico-cortical connectivity

To assess the performance of the ICA and null-coherence approaches, we calculated the power spectra of the EEG_{NC} and EEG_{ICA}. We also quantified cortico-cortical connectivity using the approach discussed in earlier works as follows: [27, 28] Let x_i , $i = 1$ to 11, denote the EEG measured in channels 1 to 11, respectively. We also denote the coherence estimated between channels x_i and x_j at frequency ω as $C_{i,j}(\omega)$. Since we have 11 channels of EEG, at each frequency this resulted in an 11×11 matrix – which we call an association matrix ($B(\omega)$). The (i, j) th element of $B(\omega)$ contains coherence between channel i and j at frequency ω . The (i, i) th element of $B(\omega)$ contains coherence of channel i with itself at frequency ω .

It should be noted that ω goes from 0 to $s/2$ in steps of $1/L$, where s is the sampling frequency in Hz and L is the Fourier transform window in units of seconds (in our case it is 3 seconds). This is a symmetric matrix and has ones along the diagonal elements. We calculated the maximum of $C_{i,j}(\omega)$ in the δ band (0.5–4 Hz) for every i, j , and called this association matrix A_δ . We defined the global connectivity index Γ_δ for the δ band by eigenvalue decomposing A_δ and summing all the eigenvalues that are greater than a predefined threshold ϵ and normalizing this summated value by the sum of all eigenvalues. We calculated ϵ by constructing a threshold matrix Θ with the same dimension as A_δ . We populated the diagonal elements with one and the off-diagonal elements with the confidence limit of the coherence (see section 2.2). The rationale behind the construction of Θ is that the statistical significance of every off-diagonal element of A_δ is determined by the corresponding element in Θ . We eigenvalue decomposed Θ and used the maximum eigenvalue as ϵ . It can be analytically demonstrated that the maximum eigenvalue of Θ is

$1 + (N - 1) \cdot (1 - [1 - \alpha]^{M-1})$, where N is the number of EEG channels, which was 11 in this work. In some scenarios, if only a very few $C_{i,j}(\omega)$ pairs showed coherence greater than the confidence limit and the rest were below the confidence limit, Γ_δ could become zero since none of the eigenvalues of A_δ would be greater than ϵ . To overcome this limitation, we

replaced the elements of A_δ that were less than the confidence limit by the confidence limit itself. With this modification, if all of the elements of A_δ were insignificant (that is, equal to the confidence limit), the maximum eigenvalue of A_δ would be equal to ϵ (indicating $\Gamma_\delta = 0$, and if any of the elements of A_δ were greater than the confidence limit, the maximum eigenvalue of would be greater than ϵ (indicating $\Gamma_\delta > 0$).

Along similar lines, we constructed association matrices A_θ , A_α , and A_β and we used them to calculate Γ_θ , Γ_α , and Γ_β for the θ (4 – 8 Hz), α (8 – 13 Hz), and β (13 – 25 Hz) bands, respectively. Furthermore, for each frequency band we identified the electrodes that contributed (spatial connectivity) to define Γ by multiplying the eigenvector of the association matrix that corresponds to the maximum eigenvalue with the maximum eigenvalue, which is the dominant principal component. Similarly, we calculated the dominant principal component for the Θ matrix and used this as a threshold to assess the statistical significance of the spatial connectivity that is the principal component of the threshold matrix. Of note, by virtue of construction the dominant principal component (threshold) calculated from is the same for all electrodes.

2.5 Validation

We simulated eleven different second autoregressive processes (AR2) to validate the null-coherence and ICA approaches. Mathematically, an AR2 process is defined as follows:

$$y[n] = a_1 y[n-1] + a_2 y[n-2] + \eta[n], \quad (5)$$

where is the AR2 process, n is the sample number, η is the driving Gaussian distributed white noise, and a_1 and a_2 are parameters of the AR2 process. An AR2 process can be thought of as a stochastic harmonic oscillator whose period T and decay time τ can be related to a_1 and a_2 as follows:[29]

$$a_1 = 2\cos\left(\frac{2\pi}{T}\right)e^{-\frac{1}{\tau}} \text{ and } a_2 = -e^{-2/\tau}.$$

We computed nine different AR2 processes y_i ($i = 2$ to 10) with T starting from 72 in-steps of two to 88 and the corresponding τ starting from 42 in-steps of two to 58. For the remaining two AR2 processes (y_1 , y_{11}), we used (T , τ) as (25,100) and (30,100). The rationale for choosing a range of parameter values was to have a high inter-channel variability. We coupled processes y_3 and y_4 as follows: $y_3 = y_3 + y_4 \cdot \sigma(y_3)/\sigma(y_4)$, and in a similar way we also coupled y_8 and y_{10} , where $\sigma(\cdot)$ denotes standard deviation. This dataset, prior to the ECG contamination, served as the ground truth (GT). We used the ECG collected from one of the newborns and added this to y_1 , y_3 , y_4 , and y_6 . To add the ECG to the AR2 processes, we followed the same methodology that we used to couple the AR2 processes. We assumed the sample rate of the AR2 processes to be 256 Hz and simulated data for 60 minutes.

2.6 Data Analysis

We partitioned the data into 10-minute windows and we attenuated the ECG using null-coherence and ICA approaches. To mitigate the volume conduction problem, we calculated the global average as the average EEG from all channels and subtracted this from the EEG of each channel. This process of re-referencing the EEG to a common average is a routine procedure used in other reports.[30, 31] For data in each 10-minute analysis window, we quantified the power spectrum and global connectivity index and the spatial cortical connection using the methods described in section 2.4. For simulated data, the ECG-free raw data served as a GT against which we compared our metrics. For neonatal data, re-referencing the data to a common average would smear the ECG into all channels. Because of this smearing problem, we expected higher cortico-cortical connectivity in the raw EEG. The method that shows the least cortico-cortical connectivity can be regarded to have attenuated the ECG completely and identified the cortical connectivity correctly. For simulated data, we used the Kolmogorov Smirnov (KS) test to compare the principal components obtained using the Raw data, the null-coherence approach and the ICA approach against GT. We compared the global connectivity index obtained from different approaches using a paired *t*-test. Multiple comparisons were adjusted using a Bonferroni correction. A value of *p* less than 0.01 was considered statistically significant.

3. Results

3.1 Numerical Simulation

A 5-second tracing of the simulated AR2 process from channels 1, 3, 4 and 6, along with the data cleaned using the null-coherence (eqn. 1–3) and ICA (eqn. 4) are shown in Figure 2. For comparison, we included the GT data for each channel (see Section 2.5). The ECG added to the raw data is shown in the last panel. The cleaned data obtained using null-coherence and ICA show no discernable ECG tracing. However, it can be noted that the data obtained using null-coherence follows the time course of the GT. Furthermore, in Figure 2, channel 1 contains a high frequency signal which is not present in channels 3, 4, and 6. However, the clean data obtained using the ICA approach for channels 3, 4, and 6 exhibit high frequency characteristics similar to the data in channel 1. To quantify the extent of deviation of the cleaned data from the GT, we calculated the root mean square difference between 1) the GT and the Raw data, 2) the GT and the data cleaned using the null-coherence approach, and 3) the GT and the data cleaned using the ICA approach. For the channels that contained ECG, the medians of the root mean square difference for the Raw data, the data cleaned using null-coherence, and the data cleaned using ICA are 40 [minimum: 20 maximum: 45], 10 [5 11], and 23 [12 25], respectively.

In Table 1, we have displayed the global connectivity index calculated in four frequency bands (δ , θ , α , and β). We calculated the dominant principal component for the GT and denoted this as (PC_{GT}). We also calculated the dominant principal component using Raw data (which is the GT contaminated with ECG) (PC_{Raw}). Furthermore, we calculated the dominant principal components for the data obtained from the null-coherence approach (PC_{NC}) as well as for the data obtained from the ICA approach (PC_{ICA}). The KS test

demonstrated that in all of the four bands, the PC_{NC} displayed $p > 0.05$, whereas PC_{Raw} and PC_{ICA} displayed $p < 0.001$.

3.2 Clinical

We retrieved EEG data from six newborns during the first hour of monitoring. Four patients had severe encephalopathy (ID# S1-S6) at presentation, one of whom (S3) died during hypothermia treatment. Two patients had moderate encephalopathy. All patients were male except for one of the severely encephalopathic infant.

3.3 Newborn EEG

Two seconds of EEG from channel C4 recorded from S3 is shown in Figure 3a. EEG_{NC} and EEG_{ICA} are shown in Figures 3b and 3c respectively, and the ECG is shown in Figure 3d. As observed in the simulated data, also in newborn EEG, the EEG_{NC} preserved the morphological features in the original data. In contrast, the EEG_{ICA} showed different morphological features from the raw data.

Power spectra estimated for EEG_{Raw} , EEG_{NC} , and EEG_{ICA} are shown in Figure 4 on the scalp locations where the electrodes were placed. Power spectra of the EEG_{Raw} showed high-frequency activity indicating ECG contamination. For data from most of the electrodes, the power spectra of EEG_{NC} and EEG_{ICA} were very similar except for the EEG from Fp1 and T3; for the data from these two electrodes the spectral power of EEG_{ICA} was lower than the spectral power of EEG_{NC} , indicating a loss of power in EEG_{ICA} .

The EEG and ECG coherence spectra are shown in Figure 5a for S1 to S6. These coherence spectra were calculated for the first 1-minute period. S1, S3, S4 and S6 had ECG contamination in 11 EEG channels. S2 had ECG contamination in 10 channels and S5 had ECG contamination only in four channels. In S2, S4, S5 and S6, the ECG contamination is highest in the high frequencies (8 – 25 Hz) whereas in S1 and S3 the contamination is observed in all frequency bands (0.5 – 25 Hz). Although, S5 and S6 had ECG contamination in the high frequency, the magnitude of the contamination was small in these subjects with S5 being the least of all. The global connectivity index Γ obtained in δ , θ , α , and β frequency bands are shown in Figure 5 (b–e), respectively. For each subject we have presented the median, lower, and upper interquartile of the global connectivity index calculated over all six 10-minute windows. Since S5 and S6 did not have high ECG contamination, the results obtained from all three datasets were almost the same. In the other two subjects (S2 and S4) that had contamination in the high frequency, Γ calculated using EEG_{NC} is different (low) from Γ calculated using EEG_{Raw} and EEG_{ICA} in the β band. In subjects (S1 and S3) that had ECG contamination in all frequency bands, the Γ calculated from EEG_{NC} is lower than that calculated from EEG_{Raw} and EEG_{ICA} . To test the performance of the different approaches, we pooled Γ from all of the subjects and compared them using a paired t-test and found that Γ obtained from EEG_{NC} was lower than that obtained from EEG_{Raw} and EEG_{ICA} in all of the frequency bands ($p < 0.01$). Between EEG_{Raw} and EEG_{ICA} , the difference was only significant in the β band; however this difference lost significance after adjusting for multiple comparisons ($p > 0.01$).

In Figure 6, we have shown the principal components obtained for EEG_{Raw}, EEG_{NC}, and EEG_{ICA} in the first, second, and third rows, respectively. We have displayed the median, lower, and upper interquartile of the dominant principal components from all subjects in each frequency band. The principal components obtained for δ , θ , α , and β bands are shown in columns one through four, respectively. Almost all the principal components were greater than the principal component calculated from the threshold (Θ) matrix. As observed in the global connectivity index (see Figure 5), the spatial distribution obtained using EEG_{Raw} and EEG_{ICA} were higher than that obtained for EEG_{NC}. The connections identified using the null-coherence approach are lowest in magnitude, followed by the ICA approach and the Raw data. This pattern is similar to what we observed in the simulated data.

4. Discussion

ECG artifacts compromise the cortico-cortical connectivity analysis using EEG. In this work, the previously developed frequency-based subtraction (null-coherence) is modified to attenuate the ECG artifacts in the neonatal EEG. For simulated data, the null-coherence approach yielded the global connectivity index that matched with that yielded from the GT data. In contrast, the global connectivity index quantified using the data obtained from the ICA approach and the Raw data did not match that obtained using the GT data. For neonatal EEG, the EEG_{NC} yielded a lower global connectivity index compared to the EEG_{Raw} and the EEG_{ICA}.

The approach proposed by Vrba et al [21] used signals from several channels as references in order to attenuate the artifacts. Neonatal clinical EEG is usually recorded with a limited number of channels. Thus, in this population it would be preferable to develop a method that does not require the loss of EEG channels that are used as reference. Hence, there was a need for a method that could use only one reference signal to attenuate the ECG artifact. We addressed this critical need by developing a null-coherence approach. Null-coherence approach assumes ECG as an input and ECG contaminated EEG as an output signal. The extent of contamination was determined using the transfer function. The Fourier transform of the ECG was weighted by the transfer function and subtracted from the Fourier transform of the EEG to obtain the clean EEG in frequency domain, which was then inverse Fourier transformed back to the time domain.

To validate the null-coherence approach, we proposed a spatio-temporal model using 11-channels of second order autoregressive processes. To assess the robustness of null-coherence and ICA approaches in attenuating the ECG artifacts and identifying the incorporated cortical connectivity, we introduced heterogeneity in the spatial channels through the coefficients of the AR2 model. The Raw data showed dominant connection between the electrodes that had ECG contamination. Although ICA attenuated the ECG artifacts to the same extent as the null-coherence approach, it showed high connections between the channels that had ECG contamination due to the redistribution problem (smearing of signals into other spatial channels). This was also evident from the higher deviations observed in the data cleaned using ICA and the Raw data from the GT.

In the ICA approach, the signals are projected from the ICA component domain to the sensor domain after nulling the component(s) that represents the interference signal. In this operation, the resulting sensor signals are a linear combination of the ICA components. Therefore, the signals from the channels that did not contain the interference signal are distributed to the channels that contained the interference signal. This effect becomes very prominent when the data in different channels have different spectral features. To demonstrate this aspect, in our simulation we generated AR2 processes with different spectral properties by adjusting the parameters of the model. As anticipated, the data obtained from the ICA approach displayed a morphology of the data in other channels, which indicates that the ICA approach suffers from the redistribution problem.

In EEG, the effect of an ECG artifact on global connectivity analysis is frequency dependent, which the null-coherence approach is able to address correctly. All three approaches, namely EEG_{Raw} , EEG_{NC} , and EEG_{ICA} , yielded consistent results when the magnitude of the ECG contamination was small. In the presence of ECG contamination, the EEG_{NC} yielded lower global connectivity index and spatial connectivity as compared to the EEG_{ICA} and EEG_{Raw} . This result is similar to what we observed for the simulated data and it may indicate that the higher connectivity observed in EEG_{ICA} could be due to a redistribution problem. The higher connectivity observed in EEG_{Raw} was due to the common ECG, which was either present in all channels in the raw data or smeared into all channels through the process of subtracting the common average to attenuate the volume conduction.

EEG has a high spatial and temporal resolution needed to perform cortico-cortical connectivity analysis. In adults, EEG connectivity analysis has been shown to successfully track brain states during anesthesia.[27] In premature infants, cortico-cortical connectivity analysis has been shown to localize brain lesions, which may escape conventional visual EEG reading.[6] In infants, cortico-cortical connectivity analysis has been shown to differentiate sleep states before the emergence of EEG signatures of sleep states.[32] To identify the cortical network reliably, the EEG should be free from artifacts. The presence of interfering sources such as ECG should be detected and attenuated prior to the quantitative EEG analysis. The null-coherence approach proposed here could be a reliable method to attenuate the ECG artifact without altering the spectral power or the morphological features of the EEG data.

Our study has several limitations. In [21] the mixing of the brain signals with cardiac signals happens in the source level and hence a dipole was used to simulate the data to test their approach. In our case, the contamination of ECG with EEG happens at the signal level, and hence we used AR2 processes to model this scenario. The presence of other artifacts, such as a sudden change in the amplitude of the EEG signals, significantly affects the performance of the proposed method. For better performance, those artifacts should be rejected prior to the null-coherence application. We fixed 3 seconds as the Fourier transform window for spectral estimation in order to reliably estimate the spectral quantities with a reasonable frequency resolution of 0.33 Hz needed for newborn EEG analysis. Other choices of window duration would yield similar results, but it would be at the expense of compromising either the spectral estimation or the frequency resolution. If after the ECG attenuation there is a

spurious change in the EEG signals between the epochs, a three-sample smoothing filter can be applied to the data at the edges of each 3-second epoch to correct this problem. Furthermore, it is not uncommon to record the brain activity of the newborns with a fewer number of electrodes in clinical settings for long-term monitoring. This smaller number of channels may not be sufficient for the ICA to reliably decompose into the independent components and this may explain the poor performance of the ICA approach for our data.

5. Conclusion

A novel frequency-based null-coherence approach that uses single reference signal to attenuate the ECG artifact is proposed. After validating the method on simulated data, testing was done on neonatal EEG signals. The null-coherence attenuated the ECG artifacts effectively and quantified the cortico-cortical connectivity reliably.

Acknowledgement

We would like to thank Ms. Sophie Wohlers for her editorial assistance.

Role of the Funding Source

This study was supported by an internal special purpose fund in the Division of Fetal and Transitional Medicine at Children's National as well as by the Award Number U54 HD090257, UL1RR031988 and KL2 RR031987 from the NIH National Center for Research Resources. We had full access to all of the data used in this study and we take complete responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Aso K, Scher MS, Barmada MA: Neonatal electroencephalography and neuropathology. *J Clin Neurophysiol* 1989, 6(2):103–123. [PubMed: 2708514]
2. Malk K, Metsaranta M, Vanhatalo S: Drug effects on endogenous brain activity in preterm babies. *Brain Dev* 2014, 36(2):116–123. [PubMed: 23422259]
3. Matic V, Cherian PJ, Koolen N, Ansari AH, Naulaers G, Govaert P, Van Huffel S, De Vos M, Vanhatalo S: Objective differentiation of neonatal EEG background grades using detrended fluctuation analysis. *Front Hum Neurosci* 2015, 9:189. [PubMed: 25954174]
4. Miller JW, Kim W, Holmes MD, Vanhatalo S: Ictal localization by source analysis of infraslow activity in DC-coupled scalp EEG recordings. *Neuroimage* 2007, 35(2):583–597. [PubMed: 17275335]
5. Schuchmann S, Schmitz D, Rivera C, Vanhatalo S, Salmen B, Mackie K, Sipila ST, Voipio J, Kaila K: Experimental febrile seizures are precipitated by a hyperthermia-induced respiratory alkalosis. *Nat Med* 2006, 12(7):817–823. [PubMed: 16819552]
6. Tokariev A, Palmu K, Lano A, Metsaranta M, Vanhatalo S: Phase synchrony in the early preterm EEG: development of methods for estimating synchrony in both oscillations and events. *Neuroimage* 2012, 60(2):1562–1573. [PubMed: 22245347]
7. Vanhatalo S, Kaila K: Development of neonatal EEG activity: from phenomenology to physiology. *Semin Fetal Neonatal Med* 2006, 11(6):471–478. [PubMed: 17018268]
8. Scher MS: Neurophysiological assessment of brain function and maturation. II. A measure of brain dysmaturity in healthy preterm neonates. *Pediatr Neurol* 1997, 16(4):287–295. [PubMed: 9258960]
9. Scher MS: Automated EEG-sleep analyses and neonatal neurointensive care. *Sleep Med* 2004, 5(6):533–540. [PubMed: 15511699]
10. Scher MS, Dokianakis SG, Sun M, Steppe DA, Guthrie RD, Sclabassi RJ: Computer classification of sleep in preterm and full-term neonates at similar postconceptional term ages. *Sleep* 1996, 19(1):18–25. [PubMed: 8650458]

11. Scher MS, Loparo KA: Neonatal EEG/sleep state analyses: a complex phenotype of developmental neural plasticity. *Dev Neurosci* 2009, 31(4):259–275. [PubMed: 19546563]
12. Hamaneh MB, Chitravas N, Kaiboriboon K, Lhatoo SD, Loparo KA: Automated removal of EKG artifact from EEG data using independent component analysis and continuous wavelet transformation. *IEEE Trans Biomed Eng* 2014, 61(6):1634–1641. [PubMed: 24845273]
13. Srivastava G, Crottaz-Herbette S, Lau KM, Glover GH, Menon V: ICA-based procedures for removing ballistocardiogram artifacts from EEG data acquired in the MRI scanner. *Neuroimage* 2005, 24(1):50–60. [PubMed: 15588596]
14. Allen PJ, Polizzi G, Krakow K, Fish DR, Lemieux L: Identification of EEG events in the MR scanner: the problem of pulse artifact and a method for its subtraction. *Neuroimage* 1998, 8(3):229–239. [PubMed: 9758737]
15. Krishnaswamy P, Bonmassar G, Purdon PL, Brown EN: Reference-free harmonic regression technique to remove EEG-fMRI ballistocardiogram artifacts. *Conf Proc IEEE Eng Med Biol Soc* 2013, 2013:5426–5429. [PubMed: 24110963]
16. Jiang JA, Chao CF, Chiu MJ, Lee RG, Tseng CL, Lin R: An automatic analysis method for detecting and eliminating ECG artifacts in EEG. *Comput Biol Med* 2007, 37(11):1660–1671. [PubMed: 17517386]
17. Scher MS, Steppe DA, Dokianakis SG, Sun M, Guthrie RD, Scialabassi RJ: Cardiorespiratory behavior during sleep in full-term and preterm neonates at comparable postconceptional term ages. *Pediatr Res* 1994, 36(6):738–744. [PubMed: 7898983]
18. Govindan RB, Massaro AN, Al-Shargabi T, Andescavage NN, Chang T, Glass P, Du Plessis A: Detrended fluctuation analysis of non-stationary cardiac beat-to-beat interval of sick infants. *EPL (Europhysics Letters)* 2014, 108:40005–p40001–p40006.
19. Comani S, Srinivasan V, Allea G, Romani GL: Entropy-based automated classification of independent components separated from fMCG. *Physics in Medicine and Biology* 2007, 52(5):N87–N97. [PubMed: 17301449]
20. Govindan RB, Massaro A, Chang T, Vezina G, du Plessis A: A novel technique for quantitative bedside monitoring of neurovascular coupling. *J Neurosci Methods* 2015, 259:135–142. [PubMed: 26684362]
21. Vrba J, McCubbin J, Govindan RB, Vairavan S, Murphy P, Preissl H, Lowery CL, Eswaran H: Removal of interference from fetal MEG by frequency dependent subtraction. *Neuroimage* 2012, 59(3):2475–2484. [PubMed: 21930216]
22. Sarnat H, Sarnat M: Neonatal encephalopathy following fetal distress. *Arch Neurol* 1976, 33:696–705. [PubMed: 987769]
23. Vrba J, Robinson SE, McCubbin J, Lowery CL, Eswaran H, Wilson JD, Murphy P, Preissl H: Fetal MEG redistribution by projection operators. *IEEE Trans Biomed Eng* 2004, 51(7):1207–1218. [PubMed: 15248537]
24. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, Fanaroff AA, Poole WK, Wright LL, Higgins RD et al.: Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med* 2005, 353(15):1574–1584. [PubMed: 16221780]
25. Halliday DM, Rosenberg JR, Amjad AM, Breeze P, Conway BA, Farmer SF: A framework for the analysis of mixed time series/point process data--theory and application to the study of physiological tremor, single motor unit discharges and electromyograms. *Prog Biophys Mol Biol* 1995, 64(2–3):237–278. [PubMed: 8987386]
26. Delorme A, Makeig S: EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods* 2004, 134(1):9–21. [PubMed: 15102499]
27. Cimenser A, Purdon PL, Pierce ET, Walsh JL, Salazar-Gomez AF, Harrell PG, Tavares-Stoeckel C, Habeeb K, Brown EN: Tracking brain states under general anesthesia by using global coherence analysis. *Proc Natl Acad Sci U S A* 2011, 108(21):8832–8837. [PubMed: 21555565]
28. Weiss D, Klotz R, Govindan RB, Scholten M, Naros G, Ramos-Murguialday A, Bunjes F, Meisner C, Plewnia C, Kruger R et al.: Subthalamic stimulation modulates cortical motor network activity and synchronization in Parkinson's disease. *Brain* 2015, 138(Pt 3):679–693. [PubMed: 25558877]

29. Timmer J, Lauk M, Pflieger W, Deuschl G: Cross-spectral analysis of physiological tremor and muscle activity. I. Theory and application to unsynchronized electromyogram. *Biol Cybern* 1998, 78(5):349–357. [PubMed: 9691264]
30. Grieve PG, Isler JR, Izraelit A, Peterson BS, Fifer WP, Myers MM, Stark RI: EEG functional connectivity in term age extremely low birth weight infants. *Clin Neurophysiol* 2008, 119(12):2712–2720. [PubMed: 18986834]
31. Williams IA, Tarullo AR, Grieve PG, Wilpers A, Vignola EF, Myers MM, Fifer WP: Fetal cerebrovascular resistance and neonatal EEG predict 18-month neurodevelopmental outcome in infants with congenital heart disease. *Ultrasound Obstet Gynecol* 2012, 40(3):304–309. [PubMed: 22351034]
32. Tokariev A, Videman M, Palva JM, Vanhatalo S: Functional Brain Connectivity Develops Rapidly Around Term Age and Changes Between Vigilance States in the Human Newborn. *Cereb Cortex* 2015.

Highlights

- A null-coherence approach is introduced to attenuate the ECG contamination in EEG
- The method is validated on simulated data
- It is applied to EEG of infants on therapeutic hypothermia for neonatal encephalopathy
- The null-coherence approach proved superior to ICA

Figure 1.
A flowchart of the various steps involved in the null-coherence approach.

Figure 2.

Five seconds of data simulated using the second order autoregressive model for channels 1, 3, 4, and 6. For each channel, the data obtained after introducing the connections but before adding the ECG signal served as the ground truth (GT). The raw data (GT + ECG) are indicated with the label '-Raw'. The data obtained from the null-coherence approach and the ICA approach are indicated with labels '-NC' and '-ICA', respectively. For comparison, the GT data (indexed '-GT') are also plotted for each channel. The ECG data added to the simulated data is shown in the last panel. The amplitude of the data is arbitrary. The unit of time is second.

Figure 3.

Two seconds of EEG recorded from S3. a) Raw tracing b) EEG cleaned using null-coherence (labeled as 'NC') c) EEG cleaned using ICA (labeled as 'ICA') and d) ECG simultaneously recorded with EEG. Both null-coherence and ICA have attenuated the ECG artifact completely. EEG obtained using null-coherence closely resembles the raw EEG tracing. In contrast, the EEG obtained using ICA has a different waveform morphology.

Figure 4.

For S3, comparison of power spectra of raw EEG, EEG obtained from null-coherence (NC), and ICA (ICA) processing. Spectra obtained for EEG from each approach are shown on the scalp locations where the electrodes were placed. Power spectra of EEG_{Raw} show high power due to ECG contamination. Power spectra calculated using EEG_{NC} and EEG_{ICA} show similar power except for Fp1 and T3; for these electrodes the spectra obtained for EEG_{ICA} showed lower power compared to the spectra obtained for EEG_{NC}.

Figure 5.

a) Coherence spectra between EEG (channels 1 to 11) and ECG for S1 to S6 are shown for the frequency band 0.5–25 Hz. The minimum and maximum values of the contour plots were set to the threshold value of the coherence and one, respectively. The global connectivity indexes (Γ) obtained for the newborn EEG in different frequency bands are displayed in b) δ , c) θ , d) α , and e) β . The data are presented as median, lower and upper interquartile over 6 measurements obtained from each of the subjects S1 to S6. The Γ values calculated using EEG_{Raw} and EEG_{ICA} are higher than the values calculated using the EEG_{NC}.

Figure 6.

The spatial connectivity quantified through the principal component using EEG_{Raw} , EEG_{NC} , and EEG_{ICA} are shown in top (PC_{Raw}), middle (PC_{NC}), and bottom (PC_{ICA}) panels, respectively. We pooled the principal components obtained from all of the subjects and calculated the median and interquartile for each band separately. For each channel, the principal components obtained for δ , θ , α , and β are shown in columns 1 to 4, respectively. The magnitude of the spatial connectivity obtained for EEG_{Raw} and EEG_{ICA} are higher compared to that of the EEG_{NC} . The horizontal dashed lines in all plots indicate the threshold calculated using the dominant principal component of the threshold matrix (see text for details).

Table 1.

Results of the simulated data obtained for the ground truth (GT), the raw data (Raw), the data cleaned using the null-coherence approach (NC) and the data cleaned using the independent component analysis (ICA) approach. The average (standard deviation) of the connectivity index Γ calculated for the six 10-minute windows in the four frequency bands.

Γ	GT	Raw	NC	ICA
δ	0.29 (0)	0.37 (0.01)	0.29 (0)	0.33 (0)
θ	0.28 (0)	0.41 (0.01)	0.28 (0)	0.38 (0.01)
α	0.29 (0)	0.46 (0.01)	0.29 (0)	0.49 (0)
β	0.29 (0)	0.50 (0)	0.29 (0)	0.41 (0.01)