Nonlinear Dynamical Analysis of the Interdependence Between Central and Autonomic Nervous Systems in Neonates During Sleep

E. Pereda · J. J. González

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Abstract We present in this paper the results of a study of the interdependence between signal characteristic of the central nervous system (electroencephalography) and the autonomic nervous system (heart rate and respiration) in human neonates during sleep. By using methods from nonlinear dynamical systems theory, we show that there exist significant differences in this interdependence with the sleep stage and the electrodes considered. This paves the way for the application of this methodology in clinical practice to study pathologies where this interdependence is altered, such as the sudden infant death syndrome.

Keywords Nonlinear interdependence analysis · Generalized synchronization · Sudden infant death syndrome · Sleep · Neonates

1 Introduction

The use of nonlinear analysis methods for the analysis of biological systems has led to important advances following theoretical results from the 1980s [1, 2], which demonstrated that the state space of a system can be reconstructed from one of the time series recorded

E. Pereda

Electrical Engineering and Bioengineering group, Department of Basic Physics,
University of La Laguna, Tenerife, Spain

E. Pereda · J. J. González

Institute of Biomedical Engineering (ITB), University of La Laguna, Tenerife, Spain

J. J. González

Laboratory of Biophysics, Department of Physiology, University of La Laguna, Tenerife, Spain
e-mail: jugonzal@ull.es

E. Pereda (✉)

Department of Basic Physics, University of La Laguna,
Avda. Astrofísico Fco. Sánchez s/n, 38205 Tenerife, Spain
e-mail: eperdepa@ull.es

from it. Since then, there have been many applications of this approach in different areas of biology and physiology (see, e.g., [3, 4] for recent reviews of neurophysiological applications). Initially, it became fashionable to assess the nonlinear characteristics of an individual signal, such as its estimated correlation dimension, largest Lyapunov exponent or entropy [5]. But recently, and following further advances in the analysis of synchronization in dynamical systems [6–8], research has expanded to include the relationship between the systems. Basically, there are two different approaches to assess the interdependence between experimental systems from nonlinear time series methods: The first one, in chronological order, entails the study of the relationship between the reconstructed state space vectors, in search for the existence of so-called *generalized synchronization* (GS) [6]. In this type of synchronization, there exists a (possibly nonlinear) relationship between the variables of systems X and Y .

As for the second approach, it entails the study of so-called *phase synchronization* (PS) [8], where a relationship between the phases of the signals exists, whereas the amplitudes may remain uncorrelated. Both approaches, although not free from practical difficulties, have been extensively used in practice [3, 4, 9]. Specifically, the GS-based approach has proven successful in determining the interdependence between electroencephalographs (EEGs) of different electrodes in humans during sleep, both in adult subjects [10] and neonates [11, 12]. In exchange for their more elaborate mathematical background – as compared to traditional linear techniques – GS- and PS-based methods are able to detect also nonlinear interdependences between the analyzed signals, thereby giving a more complete picture of the process under study.

An interesting problem in human physiology, which has received much attention in recent years, is the interdependence between central and autonomic nervous systems [13–18]. A recent study in rats using the PS approach [19] suggests that the study of such interdependence can be also carried out from the nonlinear perspective. However, there are no results hitherto about the application of the GS approach to this problem. Additionally, it is also unknown whether signals recorded from human neonates can be studied in the same way, which, in case of a positive answer, would be relevant for the possible application of this methodology in clinical practice.

The objective of this work is to determine whether such application is indeed possible, by using nonlinear interdependence indexes based on the GS concept to study the interdependence between EEG and the heart rate and respiratory activity in human healthy neonates during sleep. This will be a first step toward the use of this approach in clinical studies of pathologies such as the sudden infant death syndrome (SIDS), where this interdependence is altered [20]. SIDS is a complex, multifactorial disorder, whose causes are not completely understood. One of the prevalent hypotheses is that of triple risk [21], which indicates that SIDS takes place when the combination of three factors occurs: high risk infants (<6 months of age, when the nervous systems are still immature), an external pathophysiological stressor (such as position in bed or low weight at birth), and a genetic predisposition. In the last case, a disturbed connectivity between the brain and the autonomic system through the brainstem has been postulated as one of the most important factors. In this study, impaired activity of serotonergic receptors may be the key factor that makes it difficult to respond to stress situations such as hypoxia [22]. Genetic tests to detect such problems are non-specific and expensive, as well as difficult to carry out in every infant at risk. Thus, the analysis of the relationship between the EEG and the autonomic nervous system from signals recorded routinely and non-invasively could be a valid alternative to help diagnose the degree of risk for an infant to suffer SIDS.

Fig. 1 A schematic representation of the process of obtaining the signals. A window (in gray) is slid along the time series and within each window, the power in each band of the EEG and the mean respiratory and cardiac frequency are calculated from the EEG (*top*), the ECG (*middle*), and the respiration (*bottom*), respectively

2 Material and Methods

2.1 Subjects

The study was carried out on a group of 16 healthy-term neonates with an average post-menstrual age of 48 ± 3 weeks. They were extracted from the large database of Collaborative Home Infant Monitoring Evaluation (CHIME), kindly made available by the Boston University School of Public Health.¹

From each subject, we have four EEG channels (bipolar derivations C3-A2, O1-A2, C4-A1, and O2-A1), sampled at 100 Hz, the electrocardiogram (ECG) the respiratory signal. In each case, three artifact-free segments with a duration of 8 min were selected for further analysis, both during active sleep (AS) and quiet sleep (QS). According to standard criteria on neonate polysomnography [23], segments were considered AS if they presented a phasic electromyogram, irregular respiration, and rapid eye movements; they were considered QS if the electromyogram was tonic, the respiration was regular, and eye movements were absent. Roughly speaking, AS can be considered equivalent to REM sleep in adult subjects, whereas QS is equivalent to non-REM sleep.

As outlined in Fig. 1, a window of 30-s length was slid along each segment with a step of 0.5 s, and for each window, we calculated the power in the frequency bands δ (0–4 Hz), θ (4–8 Hz), α (8–12 Hz), and β (12–25 Hz) of the EEG and the mean frequencies of both the cardiac and the respiratory signal (CF and RF, respectively). Thus, we obtained time series of the power and the frequencies with an approximate length of about 1,000 samples. The possibility of obtaining longer time series was precluded by the requirement of stationarity of the analyzed data imposed by the methods.

2.2 Nonlinear Interdependence Index

First of all, the time series mentioned above were used to construct delayed vectors of the form:

$$\begin{aligned} x_n &= (x(n), x(n + \tau), \dots, x(n + (m - 1)\tau)) \\ y_n &= (y(n), y(n + \tau), \dots, y(n + (m - 1)\tau)). \end{aligned} \quad (1)$$

¹Web site: <http://dccwww.bumc.bu.edu/ChimeNisp/>.

In this equation, τ is the delay time (estimated as the first minimum of the mutual information function of each signal [24]) and m is the embedding dimension, estimated from an improved version of the false nearest neighbor algorithm [25]. In both cases, we made use of the TISEAN package, version 3.0.1 [26].

The interdependence between the power of the EEG in each band and each of the two signals from the autonomic system was assessed by using the nonlinear index $N(X|Y)$ [27]. It measures the relationship between signals X and Y as follows:

$$N(X|Y) = \frac{1}{N} \sum_{n=1}^N \frac{R_n(X) - R_n^k(X|Y)}{R_n(X)}. \quad (2)$$

In this equation, $R_n(X)$ is the average distance between each reconstructed vector x_n (Eq. 1), and $R_n^k(X|Y)$ is the average distance between each reference vector and its k mutual neighbors (k must be greater than m [10]). The mutual neighbors of x_n are those vectors that are simultaneous to the nearest neighbors of y_n and therefore bear the same time indices (for details, see e.g. [27]). Basically, the index N assesses whether similar temporal patterns – either linear or nonlinear ones – appear at similar times in X and Y . It ranges between 0 (independent signals) to 1 (completely synchronized signals) and is robust against differences in the complexity of X and Y , which affect other similar indexes [10, 27]. It is also asymmetric [i.e., in general $N(X|Y) \neq N(Y|X)$], although it is not possible to extract information about the direction of the interdependence only from this fact.

2.3 Bivariate Surrogate Data

To be sure that the values of the index are actually due to the interdependence between the signals, we made use of a multivariate variant of the surrogate data method [10, 28]. In this variant, one of the signal (X) is left unchanged, while several surrogate versions of the original Y are generated, which share most of its properties but are independent of X by construction. If we construct $l = 19$ of these surrogates, we can affirm, with an error probability of a 5%, that index N is detecting interdependence if and only if it is greater for the original pair than for any of the pairs $X - Y_l$ ($l = 1, \dots, 19$). For details of this methodology, see also [29] or Appendix I in [3].

Only those segments showing significant interdependence were included in the analysis.

2.4 Statistical Comparisons

We test for differences in the values of the index $N(X|Y)$ between the two sleep stages by using a two-way analysis of variance test, with the sleep stage as the independent factor and the electrodes as dependent factor. Post-hoc comparisons were carried out with a Tukey test. Each frequency band was analyzed separately; thus, it is necessary to apply Bonferroni corrections to account for the multiple comparisons. Therefore, differences were considered significant when $p < 0.05/4 = 0.0125$.

3 Results

Figure 2 shows an example of the analyzed time series. No similarity between the power in the frequency band shown and either the RF or the CF is apparent to the naked eye, except

Fig. 2 An example of the variability time series obtained from the procedure described in Section 2. Each panel corresponds to one of the subjects during AS. Total power in the δ band (in arbitrary units) is shown for each EEG electrode. The arrow points to an event in the occipital electrodes that is also apparent in the CF signal around 200 s

a prominent peak at around 200 s in the power of the occipital electrodes, which takes place at the same time that a decrease of the CF.

$N(X|Y)$ was always close to zero, and its value was not even significant in many of the segments, according to the results of the surrogate data. However, there were two bands that showed significant differences between the two sleep stages. For the CF, the δ band showed differences for the occipital electrodes, with the AS showing a greater interdependence than the QS (Fig. 3 shows this result for the O2 electrode). Additionally, for the RF, both the δ and the α band presented a greater interdependence for the AS for the occipital electrodes (Fig. 4). Overall, the results indicate that, although the interdependence is rather weak, it is detectable by the index and different in some cases for both sleep stages. Differences are clearer for the occipital electrodes.

4 Discussion

The results of this study shed light upon the question we posed in Section 1 as to whether nonlinear interdependence analysis methods based on the GS concept can be used to study the relationship between the EEG and signals from the autonomic nervous system

Fig. 3 Interdependence index N between the power in the δ band and the CF for the O2 electrode. $*p < 0.0125$ for the difference between both sleep stages

in neonates. Indeed, the methodology detected significant interdependence mainly between occipital electrodes and both the RF and CF signals as well as differences between the two sleep stages analyzed. These results agree with recent studies on adult subjects using related methods [13–15]. However, the interdependence was not significant in many cases, which strongly suggests that it is generally complicated to address this problem with the use of these signals. All in all, there were significant differences between sleep stages, with a decreased degree of correlation in QS as compared to AS, indicating that, in the former stage, there is a partial disconnection between the autonomic and the central system. This question is indeed interesting because it not only agrees with current knowledge about this issue (see, e.g., [30] and [15, 16] for results in adults) but also because it is known that, for instance, most of the changes in the SIDS syndrome occur during QS (see, e.g., [20]). We have also found differences between both sleep stages in human neonates using this methodology [12], although in this case we only analyzed central nervous system activity from multivariate EEG records.

However, further research is necessary before we can claim that this approach has clinical usefulness. Thus, it would be interesting to analyze whether the interdependence between the analyzed signals changes as a function of age (the so-called maturational

Fig. 4 As in Fig. 3 but in this case for the index N between RF and δ (left) and α band (right) of the O2 electrode. Again, $*p < 0.0125$ for the difference between both sleep stages

effect, which affects both the interdependence between EEGs in neonates [11] and the connection between heart rate and respiration [31]). Another important issue to clarify is whether prematurity or any other potential risk factor of SIDS – such as low birth weight – also modifies this interdependence and could be detected by this approach. In this same line, we are currently investigating whether siblings of SIDS victims, a group of neonates with a greater risk of sudden death than the average neonate, also present decreased interdependence between EEG and CF/RF. This is the expected result if the abovementioned genetic factor actually affects the central-autonomic relationship.

In conclusion, we think that the proposed methodology might provide further insight into the mechanisms mediating the coordination between different biological control systems even from signals recorded non-invasively in human subjects.

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